

P0

Definition

A major protein component of the insulating myelin sheath around axons of the peripheral nervous system.

► Protein Zero

P2

Definition

Event-related brain potential approximately 150–250 ms after a stimulus during wakefulness. The P2 is linked to the N1 component, is reported to be elicited by attended and non-attended stimuli, and its amplitude is reported to be associated with the intensity of the eliciting stimulus, yet the amplitude is reported to be reduced in response to attended stimuli.

► Sleep – Motor Changes
► Sleep – Sensory Changes

p53

Definition

This is a transcription factor important for cell cycle regulation. p53 was one of the first tumour suppressor genes identified. p53 gene mutations are frequently identified in a variety of cancers.

► Chromatin Immunoprecipitation and the Study of Gene Regulation in the Nervous System

p75

► Brain Inflammation: Tumor Necrosis Factor Receptors in Mouse Brain Inflammatory Responses

P300

Definition

Event-related brain potential approximately 300 ms after a stimulus during wakefulness when stimuli are both detected and attended.

► Sleep – Motor Changes
► Sleep – Sensory Changes

P Element

Definition

P element – transposable elements are a heterogeneous class of genetic elements that can move and insert at new locations on a chromosome. P elements contain terminal inverted repeat sequences and encode the protein transposase to allow for integration into the genome.

► GAL4/UAS

p38 MAPK

Definition

p38 MAPK is a member of mitogen-activated protein kinase (MAPK) family. The name MAPK was given,

because another member of the family extracellular signal-regulated kinase (ERK) was first recovered as a kinase activity in the cytosol of EGF-treated cells. Later, MAPK has been found to operate in three pathways: ERK, p38, and c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK). p38 MAPK is a kinase of 38 kDa that responds to stress condition such as tumor necrosis factor- α (TNF α), UV, and H₂O₂.

- Microglial Signaling Regulation by Neuropeptides
- Mitogen Activated Protein Kinase (MAPK)

p50 (NFKB1)

- Nf- κ B – Potential Role in Adult Neural Stem Cells

p65 (RelA)

- Nf- κ B – Potential Role in Adult Neural Stem Cells

PACAP

Definition

Pituitary adenylyl cyclase activating peptide; a neuropeptide expressed in nervous system where it functions to regulate cellular communication. PACAP has emerged as a likely retinal messenger to the suprachiasmatic nucleus (SCN), acting in concert with glutamate to communicate photic information to the circadian system. PACAP-like immunoreactivity is found in terminals of retinal ganglion cells (RGCs) innervating the SCN and two of the receptors sensitive to PACAP (PAC1 and VPAC2) are expressed in the SCN. To date, all of the available evidence indicates that the PAC1 receptor is responsible for mediating the effects of PACAP on SCN neurons.

Mechanistically, PACAP pre-synaptically enhances the release of glutamate onto SCN neurons and postsynaptically enhances the magnitude of the response to glutamate within the SCN. PACAP can also increase calcium in SCN neurons by causing a release

from intracellular stores as well as an enhancement of voltage-dependent calcium currents. Increasing calcium has the consequence of activating the mitogen-activated protein kinase (MAPK) signaling cascade and increasing transcription. At a systems level, application of PACAP can shift the phase, or alter the magnitude of glutamate-induced phase shifts, in the circadian rhythm of SCN neuronal firing in a brain slice preparation. Similarly, microinjections of PACAP into the SCN region in vivo can cause phase shifts. Administration of a PACAP receptor antagonist or an antibody against PACAP attenuates light-induced phase delays. The circadian system of mice deficient in PACAP or the PAC1 receptor exhibit altered behavioral responses to light. Overall, these studies point to a role for PACAP in increasing the functional coupling between the melatonin-containing RGCs and the retino-recipient subpopulation of SCN neurons.

- Circadian Rhythm
- Melanopsin
- p38 MAPK
- Phase Response Curve (PRC)
- Retinal Ganglion Cells
- Suprachiasmatic Nucleus (SCN)

Pacemaker

Definition

In a rhythmically active neuronal network, the neuron or neurons that have the major role in generating the rhythm. These may exhibit spontaneous oscillations of their membrane potential leading to action potentials that are very nearly equally spaced (endogenous bursting neurons), or a mutually excitatory set of neurons. An oscillator in a multi-oscillatory system entrains the other oscillators in the system, and so sets their phase relative to the pacemaker's phase, as well as forcing each oscillator's period to equal that of the pacemaker. An entrained oscillator's phase may lead or lag (occur either earlier or later than) that of the pacemaker, depending on the type of coupling (inhibitory or excitatory) and the relative periods of the oscillators in the system. Experimental proof that an oscillator can behave as a pacemaker in a physiological system is provided when transplantation confers the period or phase of the donor to the reconstituted system.

- Stomatogastric Ganglion
- Tonic Activity of Sympathetic Nerves

Pacemaker Neurons

► Bursting Pacemakers

Pacemaker Potential

Definition

An intrinsically generated rhythmic membrane fluctuation that is caused by voltage-dependent and voltage-independent ion fluxes. A pacemaker potential that gives rise to action potentials is called a pacemaker “burst.” Synonym for pacemaker potential: “drive potential.”

► Bursting Pacemakers

Pacinian Corpuscle

Definition

Pacian corpuscles are the largest cutaneous mechanoreceptors, but are also found in deep structures (e.g., abdominal mesentery). They are exquisitely sensitive to light mechanical stimuli, including high frequency vibration (>60 Hz).

► Vibration Sense

► Pacinian Corpuscle Regeneration

Pacian Corpuscle Regeneration

CHIZUKA IDE

¹Department of Anatomy and Neurobiology, Kyoto University Graduate School of Medicine, Yoshidakonoe-cho, Sakyo-ku, Kyoto, Japan;

²Department of Occupational Therapy, Aino University Faculty of Nursing and Rehabilitation, Shigashiohta 4-5-4, Ibaragi City, Osaka, Japan

Synonyms

Vater-Pacini corpuscle; Vater-Pacini’s corpuscle; Pacini corpuscle; Pacini’s corpuscle; Pacinian corpuscle; Corpusculum lamellosum

Definition

The Pacinian corpuscle is the largest ellipsoidal sensory corpuscle functioning as a very rapidly adapting mechanoreceptor. It consists of one straight axon terminal extending at the center of the corpuscle along its long axis, the inner core surrounding the axon terminal, and the outer core occupying the outermost part of the corpuscle.

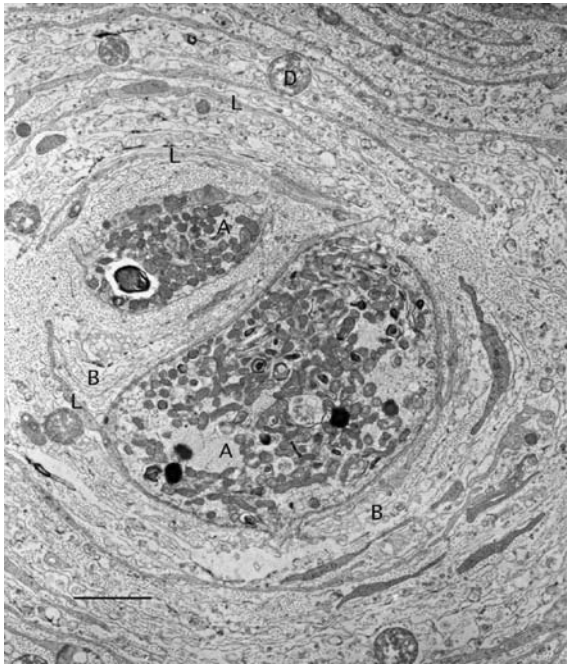
Characteristics Structure

The Pacinian corpuscle is ellipsoidal in shape, measuring 0.2–1 mm at the long axis, and can be seen by the naked eye in dissection. It is found in connective tissues of the subcutaneous layer, joint capsule and periosteum. The corpuscle is innervated by a single thick myelinated axon that ends as a straight axon terminal in the center. The axon terminal is sandwiched by hemicircular inner cores, so that the axon terminal is oval in cross section [1]. The inner core consists of stacks of numerous thin cytoplasmic processes of specialized Schwann cells. The outer core is composed of loose lamellae of modified perineurial cells. The inner core cells express p75 and TrkB, while the outer core cells express only p75 [2]. Small axoplasmic protrusions are formed at the oval edges as well as at the extreme end of the axon terminal. These protrusions are considered to be the site of mechano-electric transduction [3].

Regeneration

Following denervation, the axon terminal disappears, and the inner core becomes somewhat atrophic but remains with the outer core for an extended period. Following re-innervation, an axon enters the corpuscle and the inner core lamellae become “active,” as in the case of the Meissner corpuscle. After regeneration, most Pacinian corpuscles are innervated by a single axon, but there are a few that receive two axons, or remain non-innervated. Some corpuscles have multi-terminals associated with inner cores, resulting partly from the branching of regenerating axon terminals [4]. Aberrant regenerating nerves other than sensory axons can enter Pacinian corpuscles [5].

Pacian corpuscles can be regenerated even in the non-cellular environment; the connective tissue scaffolds of the Pacinian corpuscle remain after the cellular components have been degraded by local freeze-treatment. A regenerating axon enters such acellular scaffolds, accompanied by Schwann cells migrating from the proximal stump (Fig 1). Schwann cells develop into inner core cells associated with axon terminals. Perineurial cells develop into outer core cells within the scaffold of the original outer core region. Although atypical in its organization, the newly regenerated corpuscle possesses the three basic components including axon terminals, inner and outer cores [6]. This indicates



Pacinian Corpuscle Regeneration. Figure 1 The periosteum of the tibia, in which numerous Pacinian corpuscles are located, was freeze-treated to kill cellular components of the corpuscle in the rat. The acellular matrix including basal laminae (B) of the corpuscle remained after the cellular components had been degraded. Regenerating axons accompanied by immature Schwann cells enter the matrix; the axon terminals (A) are situated at the center of the matrix and Schwann cells extend thin cytoplasmic lamellae (L) along the basal lamina scaffolds around axon terminals with a pattern similar to that of the normal corpuscle. New Pacinian corpuscles, although atypical in overall cellular structure, can develop in the acellular matrix of the old corpuscle. (D) cell debris. Scale bar: 2 μ m.

that the acellular matrix of the Pacinian corpuscle has the ability to induce the innervating axons, Schwann cells and perineurial cells to develop into axon terminals, inner core cells, and outer core cells, respectively.

References

1. Munger BL, Yoshida Y, Hayashi S, Osawa T, Ide C (1988) A re-evaluation of the cytology of cat Pacinian corpuscle. I. The inner core and clefts. *Cell Tissue Res* 253:83–93
2. Stark B, Risling M, Carlstedt T (2001) Distribution of the neurotrophin receptors p75 and trkB in peripheral mechanoreceptors; observations on changes after injury. *Exp Brain Res* 136:101–107
3. Ide C, Hayashi S (1987) Specialization of plasma membrane in Pacinian corpuscles: Implications for mechanoelectric transduction. *J Neurocytol* 16:759–773

4. Zelena J, Zacharova G (1997) Reinnervation of cat Pacinian corpuscles after nerve crush. *Acta Neuropathol* 93:285–293
5. Zelena J, Jirmanova I, Lieberman AR (1990) Reinnervation of transplanted Pacinian corpuscles by ventral root axons: Ultrastructure of the regenerated nerve terminals. *J Neurocytol* 19:962–969
6. Ide C (1987) Role of extracellular matrix in the regeneration of a Pacinian corpuscle. *Brain Res* 413:155–169

Paciniform Endings

Definition

Small mechanoreceptors resembling Pacinian corpuscles, located in the deeper regions of the dermis of glabrous skin.

- [Pacinian Corpuscle](#)
- [Vibration Sense](#)

Paedomorphosis

Definition

The brains of amphibians appear to be much simpler than those of other vertebrates. Lissamphibians, i.e., living amphibians, have undergone secondary simplification, which arises from paedomorphosis, a form of heterochronic evolution. This process has affected the three amphibian orders differently: anurans appear to be least and salamanders most paedomorphic, while caecilians exhibit an intermediate degree of paedomorphosis.

It commonly involves different degrees of retardation, reduction or absence of traits in otherwise fully developed organisms when compared with phylogenetic outgroups. Thus, a mosaic of fully adult traits, weakly expressed traits, and missing characters appears in terminal ontogenetic stages. Accordingly, amphibian brains are expected to have fewer cells, a lower degree of morphological differentiation of cells, and reduced migration, but retain the plesiomorphic structural, functional and developmental organization found among other vertebrates.

- [Evolution of the Visual System: Amphibians](#)

PAG

Definition

►Periaqueductal Gray Matter (PAG)

►Pain Imaging

Pain

G. F. GEBHART

Center for Pain Research, University of Pittsburgh,
Pittsburgh, PA, USA

Introduction

Pain is appreciated to be a complex sensory experience, characterized by both discriminative and emotional/cognitive dimensions. Moreover, the peripheral and central nervous system components that comprise the pain “network” are highly plastic, meaning that neural and non-neural constituents undergo changes in behavior and excitability in painful conditions. Thus, tissue insult commonly leads to changes in either or both the quality and intensity of perceived stimuli, typically beginning at peripheral sites and including central components in persistent pain states.

Stimuli that evoke pain are termed noxious and the peripheral sensory receptors/transduction sites acted upon by ►noxious stimuli are termed ►nociceptors. Input from nociceptors is widely distributed throughout the central nervous system and can evoke simple ►nociceptive reflexes that are organized at the level of the spinal cord (e.g., ►nociceptive withdrawal reflexes), engage ►autonomic centers in the brainstem that increase heart rate and blood pressure, or lead to expression of emotional-affective responses that can be influenced by gender, age, previous experience, ►stress and mood (among other factors) (►Emotional/affective aspects of pain; ►Pain in older adults; ►Pain in children; ►Gender/sex difference in pain).

More than 100 years ago, Sherrington [1] advanced the operational definition of a noxious stimulus and anticipated by decades the discovery of sensory receptors (nociceptors) in skin that responded only to noxious intensities of stimulation. Sherrington’s experimental work established that mechanical, thermal or chemical stimuli that damaged or threatened damage to skin were *adequate* for activation of nociceptors to cause pain. We know now that adequate noxious stimuli differ for skin, muscle, joints and internal organs, and also that some nociceptors can be activated by low-threshold stimuli,

revealing the importance of encoding of stimulus intensity by peripheral sensory receptors (►Cutaneous pain, nociceptor and adequate stimuli). For example, cutting, crushing or burning stimuli, which reliably produce pain when applied to skin, are not reliable noxious stimuli when applied to internal organs. Pain arising from internal organs is more commonly produced by over-distension, traction on the mesenteries, ischemia or inflammation (e.g., appendicitis). Similarly, adequate noxious stimuli for muscle and joints, which also are not exposed to the external environment, include chemicals typically associated with inflammatory processes. In further distinction from skin, deep pain such as arises from muscle and viscera are relatively poorly localized and commonly referred to other sites, including overlying skin and muscle. The clinical presentation and characteristics of muscle pain (►Muscle pain including fibromyalgia), ►joint pain (►Joint pain, nociceptors and adequate stimuli) and ►visceral pain are discussed in detail in essays in this section of the Encyclopedia (see also ►incisional/post-op pain; ►Low back/spine pain).

As indicated above, tissue insult commonly alters either the quality and/or intensity of applied stimuli. Hyperalgesia (an increased response to a stimulus which is normally painful) and allodynia (pain due to a stimulus which does not normally provoke pain [►Hyperalgesia and allodynia]) represent increases in the excitability of nociceptors (hyperalgesia) and activation of low-threshold mechanoreceptors (allodynia – by mechanisms not fully understood), respectively. Increases in excitability of nociceptors have been documented to arise from changes in ►voltage-gated ion channels (e.g., ►Ca²⁺ channels, ►K⁺ channels and ►Na⁺ channels [►Voltage-gated ion channels and pain]) and ►ligand-gated channels and receptors (e.g., transient receptor potential [TRP] channels (►TRP channels), purinergic receptors, including both P2X and P2Y, etc. [►G-protein coupled receptors (GPCRs) in sensory neuron function and pain]). Such changes can be initiated by a variety of peripheral mediators, including those associated with inflammation (e.g., ►prostaglandins, protons, etc. [►Inflammatory pain]), ►growth factors (►Growth factors and pain) and the ►immune system (►Immune system and pain). Typically, increased excitability of nociceptors (for example produced by inflammatory mediators) is relatively short-lived and reversible. However, these changes can persist, such as occurs in ►autoimmune diseases characterized by dysregulation of an immune response or following tissue insult early in life. ►Rheumatoid arthritis, ►multiple sclerosis and some viral infections can produce ►chronic pain that is difficult to manage.

After nociceptor neurogenesis and maturation (►Development of nociception) [2], tissue damage in the neonatal period can lead to increased pain

sensitivity [3] and exaggerated responses to noxious stimuli in adult non-human animals well after the early insult has fully recovered. For example, organ insult in neonatal animals [4,5], skin incisions/surgery as well as stressful events (e.g., maternal separation [6]; all have been shown to lead to increased sensitivity to noxious stimuli in adult life. This increased sensitivity is not always apparent when acute noxious stimuli are tested, but is clearly evident when tissue is re-inflamed or injured.

These peripheral events, whether introduced early in life or produced in adults, have far-reaching central consequences. ▶Sensitization (increased excitability of nociceptors [7]; leads to changes in excitability of neurons in the spinal cord as well as sites rostral in the brain. By analogy to the periphery, increases in the excitability of spinal and supraspinal neurons is referred to as “central sensitization” [8]. The initial impetus for the increase in excitability of central neurons arises from the increased input from peripheral nociceptors, including ▶silent nociceptors (▶Nociceptors and characteristics) [9], and increased release of ▶neurotransmitters from their central terminals. Central sensitization, either at the level of the spinal cord or at supraspinal sites, represents plasticity of central neurons, which apparently can be sustained well beyond recovery from the peripheral insult.

At the level of the spinal cord, because of similarities in neurotransmitters released from nociceptor terminals and characteristics of neuron response properties, central sensitization shares characteristics with learning (▶Synaptic long-term potentiation (LTP) in pain pathway). At supraspinal sites, nociceptive input is widely distributed to sites important for the discriminative aspects of pain (e.g., location, duration and intensity) (▶Ascending nociceptive pathways) and also to brain areas associated with emotion and cognition (▶Pain imaging; Emotional/affective aspects of pain). This nociceptive input also influences sites in the brainstem important to descending control of spinal input (▶Descending modulation of nociception). Descending influences from the midbrain and medulla were initially believed to be principally, if not exclusively, inhibitory in nature and selective for nociceptive input. We now know that descending influences can contribute to chronic pain states, either by reduced descending inhibition or active facilitation of spinal input and, moreover, and are not selective for spinal nociceptive input, but also modulate non-noxious (innocuous) spinal input. Indeed, it is now considered that chronic disorders such as functional gastrointestinal diseases, ▶fibromyalgia, etc. may be contributed to by disordered descending modulation of spinal input.

In addition to the nociceptive component of the experience of pain (e.g., activation of nociceptors, spinal pathways, mechanisms of peripheral and central sensitization, etc.), nociceptive input at supraspinal sites

also engages emotional, affective and cognitive dimensions of pain (Emotional/affective aspects of pain). That supraspinal influences can be potent is attested to by the ▶placebo analgesic response, in which expectancy has been identified as the most relevant psychological mediator. Expectancy can be manipulated by verbal instruction or by conditioning. The discriminative dimension of pain is associated with ▶thalamic and ▶somatosensory cortex and ▶motor cortex whereas the emotional/affective dimension of pain activates the amygdala, cingulate gyrus and ▶prefrontal cortex (Pain imaging). Brain imaging has thus confirmed and extended our anatomical understanding of the discriminative and emotional/cognitive anatomical dimensions of the experience of pain. Interestingly, both the discriminative and emotional/cognitive dimensions of pain may be sexually dimorphic. A growing literature reveals differences between males and females with respect to sensitivity to noxious stimuli as well as to the ability to tolerate pain (▶Gender/sex differences in pain). Women access physicians for pain-related problems far more frequently than do men, and while there may be many reasons why this is so, one contributing factor certainly relates to distinct differences in responses to noxious stimuli, likely contributed to by hormonal influences.

Despite our significantly increased knowledge about pain and pain mechanisms, there remain significant challenges in several areas. ▶Neuropathic pain, including ▶central pain, arises from damage to the nervous system, either in the periphery or centrally. Unlike *inflammatory pain*, damage to the nervous system results in pain commonly produced by normally innocuous stimuli (i.e., touch-evoked pain, or allodynia), which is difficult to manage. Pain in neonates (Development of nociception) and children (Pain in children), as well as pain in older adults, including those with ▶dementia (Pain in older adults), similarly present challenges in terms of both pain assessment/measurement (▶Pain psychophysics) and pain management. It was incorrectly assumed until relatively recently that the nociceptive system was undeveloped or underdeveloped in neonates and, accordingly, that they did not feel pain (Development of nociception; Pain in children) or require analgesia or anesthesia. This flawed thinking has fortunately been corrected and we now know that untreated, unattended pain in neonates and young children can lead to long-term changes in responses to noxious stimuli. Because young children and adults with dementia cannot effectively communicate their pain, they too tend to be under-treated.

In the United States, pain accounts for 20% of patient visits to physicians and 10% of prescription drug sales [10], figures likely comparable to those in many other countries (but not including those where governments restrict access to analgesic drugs, and unrelieved pain is

commonplace). Pain management can be daunting for health care providers, even with access to all available drugs and management strategies. As recounted in the essays in this section of the Encyclopedia, significant progress has been achieved in understanding mechanisms underlying painful disease conditions, with consequent improvement in pain management.

References

1. Sherrington CS (1906) The integrative action of the nervous system. Charles Scribner's Sons, New York
2. Woolf CJ, Ma Q (2007) Nociceptors – noxious stimulus detectors. *Neuron* 55:353–364
3. Hermann C, Hohmeister J, Demirakca S, Zohsel K, Flor H (2006) Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* 125:278–285
4. Al-Chaer ED, Kawasaki M, Pasricha PJ (2000) A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. *Gastroenterol* 119:1276–1285
5. Randich A, Uzzell T, DeBerry JJ, Ness TJ (2006) Neonatal urinary bladder inflammation produces adult bladder hypersensitivity. *J Pain* 7:469–479
6. Coutinho SV, Plotsky PM, Sablad M, Miller JC, Zhou H, Bayati AI, McRoberts JA, Mayer EA (2002) Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol* 282:G307–G316
7. Bessou P, Perl ER (1969) Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol* 32:1025–1043
8. Ji R-R, Woolf CJ (2001) Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. *Neurobiol Dis* 8:1–10
9. Schaible H-G, Schmidt RF (1984) Effects of an experimental arthritis on the sensory properties of fine articular afferent units. *J Neurophysiol* 54:1109–1122
10. Max MB (2003) How to move pain and symptom research from the margin to the mainstream. *J Pain* 4:355–360

Pain, Neuropathic

Definition

►Neuropathic Pain

Pain among Seniors

►Pain in Older Adults (Including Older Adults with Dementia)

Pain and Growth Factors

►Growth Factors and Pain

Pain and Immune System

►Immune System and Pain

Pain and Ligand-gated Channels/Receptors

►G-Protein Coupled Receptors in Sensory Neuron Function and Pain

Pain and Voltage-gated Ion Channels

►Voltage-Gated Ion Channels and Pain

Pain Distress

►Emotional/Affective Aspects of Pain

Pain Emotion

Definition

Or pain emotional component. The emotional reactions and feeling states associated with thoughts (cognitions) about pain, such as anxiety, depression, fear, and despair. These feeling states involve thoughts about the present, past and future, and are distinct from the immediate feelings of pain unpleasantness that motivate

or inhibit behaviors and that are similar to other immediate feelings such as hyperthermia or the urge to breathe.

► Emotional/Affective Aspects of Pain

Pain Hypersensitivity

► Hyperalgesia and Allodynia

Pain Imaging

IRENE TRACEY

Department of Clinical Neurology and Nuffield Department of Anaesthetics, Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, UK

Definition

Pain imaging is the capacity to identify functionally relevant neuronal activity within the central nervous system (brain and spinal cord) correlated with the subjective experience of pain. Imaging relates principally to studies in humans, but not exclusively. Different technologies provide this capability to image pain with varying degrees of invasiveness, spatial and temporal resolution.

Characteristics

Why Image Pain?

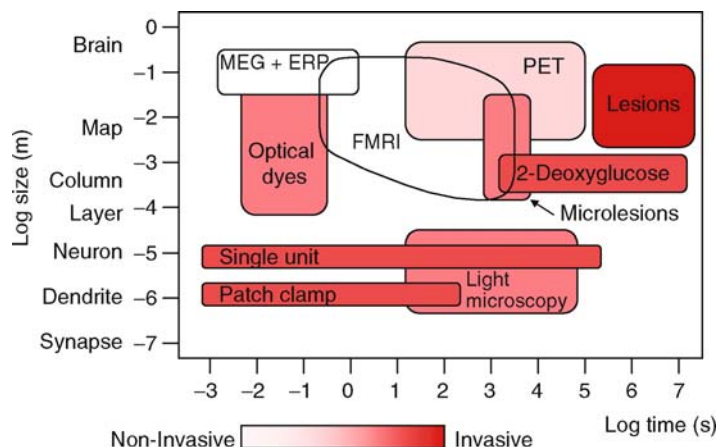
Most neuroimaging methods provide a non-invasive, systems-level understanding of the central mechanisms involved in pain processing. To date, the focus has been to dissect the physiological, psychological and cognitive factors that influence nociceptive inputs to alter pain perception in healthy subjects and patients suffering from chronic pain. Obtaining reliable objective information related to the individual's subjective pain experience provides a powerful means of understanding not only the central mechanisms contributing to the chronicity of pain states, but also potential diagnostic information. Identifying non-invasively where plasticity, sensitization and other amplification processes might occur along the pain neuraxis for an individual, and relating this to their specific pain experience or measure of pain relief, is of considerable interest to the clinical pain community and pharmaceutical industry. This is why imaging pain is useful.

Imaging the Brain – Methods Available

Figure 1 illustrates the main imaging modalities in use today and what physiological correlate of brain activity they measure. There is a “cost” or balance between the spatial and temporal information achievable and how “invasive” you have to be if you want high resolution in both domains. Therefore, when choosing your imaging modality, pros and cons must be considered, dependent upon your hypothesis and goal. Other methods provide different sorts of information about the brain (i.e., structural or metabolic rather than functional), and these newer ways of examining the human brain are providing exciting and highly novel information about pain processing.

Pain as a Perception

Pain is a conscious experience, an interpretation of nociceptive inputs influenced by memories, emotional,



Pain Imaging. Figure 1 A schematic displaying the relationship between the spatial and temporal resolution, as they relate to non-invasiveness, for the main current imaging tools.

pathological, genetic and cognitive factors. Resultant pain is therefore not always related linearly to nociceptive drive or input, neither is it solely for vital protective functions; this is especially true in, chronic pain states. Furthermore, the behavioral response of a subject to a painful event is modified according to what is appropriate or possible in any particular situation. Pain is, therefore, a highly subjective experience. Figure 2 illustrates the mixture of physical, cognitive and emotional factors that influence nociceptive inputs to amplify, attenuate and color the pain experience.

Clearly, the majority of factors influencing pain percepts are centrally mediated and our ability to unravel and dissect their contribution has only been feasible since neuroimaging allowed us non-invasive access to the human CNS. Determining the balance between peripheral versus central influences, and ascertaining which are due to pathological versus emotional or cognitive influences, will clearly aid decisions regarding the targeting of treatments (i.e., pharmacological, surgical, cognitive behavioral or physical rehabilitation). This is perhaps where imaging might provide its greatest contribution in the field of pain.

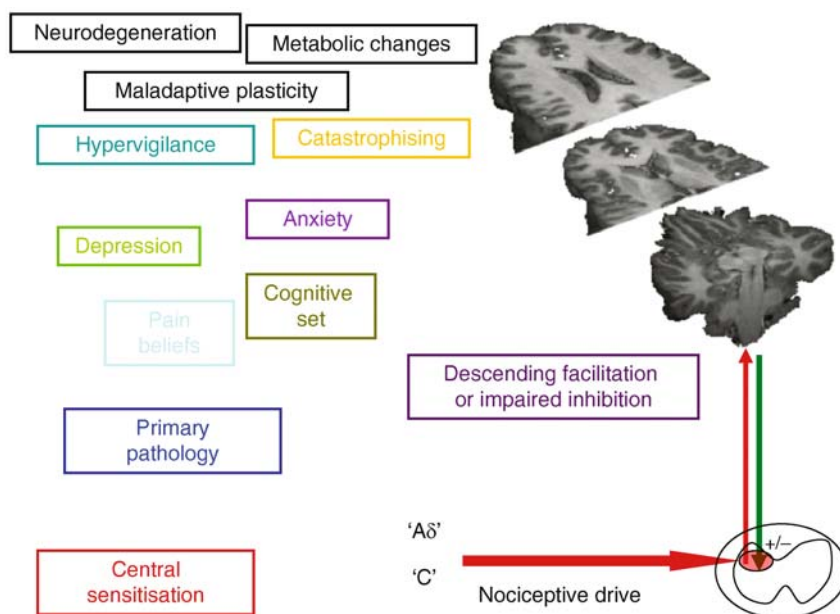
The “Cerebral Signature” for Pain Perception

Because pain is a complex, multifactorial subjective experience, a large distributed brain network is accessed during nociceptive processing; this is often called the “pain matrix” and simplistically can be thought of as having lateral components (sensory–discriminatory, involving areas such as primary and secondary somatosensory cortices, thalamus and posterior parts of

insula) and medial components [affective–cognitive–evaluative, involving areas like the anterior parts of insula, anterior cingulate cortex (ACC) and prefrontal cortices]. However, because different brain regions play a more or less active role depending upon the precise interplay of the factors involved in influencing pain perception (e.g., cognition, mood, injury, and so forth), the “pain matrix” is not a defined entity [1]. A recent meta-analysis of human data from different imaging studies provides clarity regarding the commonest regions found active during an acute pain experience as measured by PET and ▶fMRI [2] (See Fig. 3).

These areas include: primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices as well as the thalamus. This is not to say these areas are the fundamental core network of human nociceptive processing (and if ablated would cure all pain), although studies investigating acute pharmacologically induced analgesia do show predominant effects on this core network, suggesting their overall importance on influencing pain perception. Other regions such as basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices can also be active dependent upon the particular set of circumstances for that individual (see Fig. 2). A “cerebral signature” for pain is perhaps how we should define the network that is necessarily unique for each individual.

To understand how nociceptive inputs are processed and altered to subsequently influence changes in the pain experienced, it is useful to separately examine the main factors listed in Fig. 2 that alter pain perception.



Pain Imaging. Figure 2 Schematic illustrating the main factors that influence nociceptive inputs to alter pain perception.

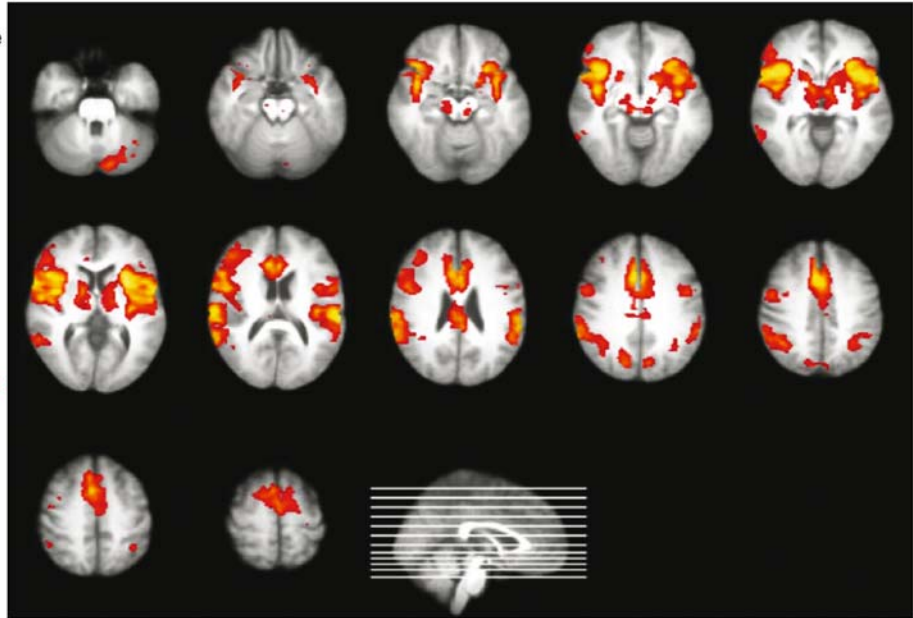
Main regions activated in response to acute nociceptive stimulation (see diagram on right):

- Spinal cord
- Thalamus
- S1 and S2
- Insula (not always same division)
- Anterior cingulate cortex (not always same division)
- Prefrontal cortex

BUT THEN ALSO perhaps:

- Amygdala
- Hippocampus
- Posterior parietal cortex
- Basal ganglia
- Brainstem
- Etc..

..depending upon the circumstances.....



Pain Imaging. Figure 3 Neuroanatomy of pain processing. Main brain regions that activate during a painful experience are highlighted as bilaterally active but with more dominant activation on the contralateral hemisphere (more yellow).

Genetics: We cannot ignore the possibility that our genes influence both how nociceptive stimuli are processed and how the brain reacts to peripheral injury and increased nociceptive inputs. Similarly, we cannot ignore the central role that our life experiences have on both these processes. Imaging studies have investigated whether individuals claiming to be more “sensitive” to pain, compared with others, activate more brain regions involved in pain perception. Early work suggests that subjects who rated the pain highest exhibit more robust pain-induced activation of ►S1, ACC, and ►PFC compared with those who rated pain lowest. The key question is whether this increased pain report and correlated objective readout is nature or nurture driven. Studies are beginning to link genetic influences on human nociceptive processing with physical processes within the brain. Zubietta and colleagues examined the influence of a common functional genetic polymorphism affecting the metabolism of catecholamines on the modulation of responses to sustained pain in humans using psychophysical assessment and ►PET [3]. Individuals homozygous for the met158 allele of the catechol-*O*-methyltransferase (COMT) polymorphism (val158met) showed diminished regional μ -opioid system responses to pain (measured using PET) and higher sensory and affective ratings of pain compared with those homozygous for the valine polymorphism. This study and others are providing

good evidence regarding how our genes influence nociceptive processing within the brain and consequently our pain experience.

Attention

We know from experience that attention is very effective in modulating the sensory and affective aspects of pain. fMRI and neurophysiological studies showed attention- and distraction-related modulations of pain-evoked activations in many parts of the pain “matrix.” From these studies, regions that appear critical during the attentional modulation of pain include the descending pain modulatory system as well as key elements of the pain “matrix.”

The descending pain modulatory system

This is a well characterized anatomical network that enables us to regulate nociceptive processing (largely within the dorsal horn) in various circumstances to produce either facilitation (pro-nociception) or inhibition (anti-nociception) [4] (see also ►Descending modulation of nociception). The pain-inhibiting circuitry, of which the periaqueductal grey (►PAG) is a part, is best known and contributes to environmental (e.g., during the fight or flight response) and opioid-mediated analgesia. There are descending pathways that facilitate pain transmission, however, and it is thought that sustained activation of these circuits may underlie some

states of chronic pain (see below). Recently, researchers have investigated whether alteration in people's attention influences brainstem activity and, therefore, nociceptive processing via cortical–brainstem influences. In an early study using high-resolution imaging of the human brainstem, we showed significantly increased activity within the PAG in subjects who were distracted compared to when they paid attention to their pain, with concomitant changes in pain ratings. Indeed, the change in pain rating between attending and distracting conditions correlated with the change in PAG activity across the group, suggesting a varying capacity to engage the descending inhibitory system in normal individuals. Further work by others has extended these observations and shown that the cingulo-frontal cortex exerts top-down influences on the PAG and posterior thalamus to gate pain modulation during distraction. These studies, and others, provide clear evidence for the involvement of brainstem structures in the attentional modulation of pain perception, and recent work using diffusion tractography confirms that anatomical connections exist between cortical and brainstem regions in the human brain, thereby enabling such top-down influences.

Placebo

Recent work in humans has helped provide a framework by which the placebo effect and subsequent analgesia is mediated (see ►[Placebo analgesic response](#)). Again, the brainstem is critically involved in mediating placebo analgesia. Descending influences from the diencephalon, hypothalamus, amygdala, ►[ACC](#) insula and prefrontal cortex that elicit inhibition or facilitation of nociceptive transmission via brainstem structures are thought to occur during placebo analgesia. Using PET, it has been confirmed that both opioid and placebo analgesia are associated with increased activity in the rostral ACC, and that a co-variation between the activity in the rostral ACC and the brainstem during both opioid and placebo analgesia, but not during pain alone, exists. Wager and colleagues extended these early observations to examine placebo expectation effects [5]. Using a conditioning design, they found that placebo analgesia was related to decreased brain activity in classic pain processing brain regions (e.g., thalamus, insula, and ACC), but was additionally associated with increased activity during anticipation of pain in the prefrontal cortex (PFC), an area involved in maintaining and updating internal representations of expectations. Stronger PFC activation during anticipation of pain was found to correlate with greater placebo-induced pain relief and reductions in neural activity within pain regions. Furthermore, placebo-increased activation of the PAG was found during anticipation, the activity within which correlated significantly with dorsolateral PFC (DLPFC) activity.

This is consistent with the concept that prefrontal mechanisms can trigger opioid release within the brainstem and, thereby, influence the descending pain modulatory system to modulate pain perception during the placebo effect.

Mood

For both chronic and acute pain sufferers, one's mood and emotional state has a significant impact on resultant pain perception and ability to cope. For example, it is a common clinical and experimental observation that anticipating and being anxious about pain can exacerbate the pain experienced. Anticipating pain is highly adaptive, but for the chronic pain patient it becomes maladaptive and can lead to fear of movement, avoidance, anxiety, and so forth. Studies aimed at understanding how anticipation and anxiety cause a heightened pain experience have been performed using imaging methods [6]. Critical regions involved in amplifying or exacerbating the pain experience include the entorhinal complex, amygdala, anterior insula and prefrontal cortices.

With regard to mood, depressive disorders often accompany persistent pain. Although the exact relationship between depression and pain is unknown, with debate regarding whether one condition leads to the other or if an underlying diathesis exists, studies have attempted to isolate brain regions that may mediate their interaction. Early studies indicated that activation in the amygdala and anterior insula appears to differentiate fibromyalgia patients with and without major depression. Another fibromyalgia study found that pain catastrophizing (defined as a set of negative emotional and cognitive processes), independent of the influence of depression, was significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral PFC), emotional aspects of pain (claustrum, closely connected to amygdala) and motor control [7]. The construct of catastrophizing incorporates magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes. The results by Gracely and colleagues support the notion that catastrophizing influences pain perception through altering attention and anticipation, as well as heightening emotional responses to pain (see ►[Emotional/affective aspects of pain](#)).

The prefrontal cortex and pain

It is clear from these few studies described above and others in the literature that pronounced PFC activation is consistently found across clinical pain conditions, irrespective of underlying pathology. We are only beginning to unravel the roles of specific PFC regions in pain perception; it is thought they reflect emotional,

cognitive and interoceptive components of pain conditions, as well as perhaps processing of negative emotions, response conflict and detection of unfavorable outcomes in relation to self. Interestingly, imaging studies attempting to capture the neural signature of the ongoing, spontaneous pain that patients commonly experience are finding increased medial PFC, including rostral ACC, activity during episodes of sustained high ongoing pain. These early data suggest a very different neural “signature” for the patient’s ongoing pain, compared to the acute nociceptive network found active in response to provoked stimulation, as described above in most fMRI studies. A specific role for the lateral PFC as a “pain control center” has been put forward in a study of experimentally induced allodynia in healthy subjects [8]. In this study, increased lateral PFC activation was related to decreased pain affect, supposedly by inhibiting the functional connectivity between medial thalamus and midbrain, thereby driving endogenous pain-inhibitory mechanisms.

It is important to also note that the PFC (specifically the dorsolateral PFC) is one site of potential major neurodegeneration and cell death in chronic pain patients. These latest findings suggest that severe chronic pain could be considered a neurodegenerative disorder that especially affects this region. However, determining what the possible causal factors are that produce such neurodegeneration is difficult. Candidates include the chronic pain condition itself, the pharmacological agents prescribed for pain management or perhaps the physical lifestyle change subsequent to becoming a chronic pain patient. Carefully controlled longitudinal studies are needed.

Pain without a nociceptive input

Recent imaging data display activity of the near entire “pain matrix” without any nociceptive input during empathy and hypnosis manipulations, suggesting it is time to reconsider how we define central pain processing with respect to the origin of the input and resultant perception and meaning. This is not to say that pain experienced without a nociceptive input (sometimes referred to as psychogenic pain) is any less real than “physically” defined pain; indeed, neuroimaging studies have highlighted the physiological reality of such experiences due to the extensive neural activation that occurs.

Injury

Recently, changes within the descending pain modulatory network have been implicated in chronic pain (central sensitization) and in functional pain disorders [9] (see also ▶[Descending modulation of nociception](#)). Changes are defined in terms of patients having either a dysfunctional descending inhibitory system or an activated and enhanced descending facilitatory system.

There has been convincing evidence advanced regarding the differential involvement of the PAG, rostroventromedial medulla (▶[RVM](#)), parabrachial nucleus (▶[PB](#)), dorsal reticular nucleus and nucleus cuneiformis (▶[NCF](#)) in the generation and maintenance of central sensitization states and hyperalgesia in both animal models and, for the first time, in a human model of secondary hyperalgesia [10]. Changes within the descending pain-modulatory network in chronic pain, in terms of patients having either a dysfunctional descending inhibitory system or an activated and enhanced descending facilitatory system, are clearly implicated in these and increasingly in other clinical studies.

Understanding which CNS areas are involved in engaging or disengaging this descending modulatory system has significant potential to not only further our understanding of how pain is perceived, but in developing mechanism-based therapies for treating different types of acute and chronic pain.

Spinal cord imaging

Clearly, to determine the extent of changes present within the CNS we must develop methods that allow noninvasive access to the changes within the human spinal cord, and these are currently being successfully developed.

Altered opioidergic and dopaminergic pathways

The availability of PET ligands for opioid and dopamine receptors has allowed the study of these receptor systems in several clinical pain states. Early opioid receptor ligand studies showed decreased binding in patients with chronic pain that normalized after reduction of their pain symptoms. Regional differences in ligand binding have recently been found in neuropathic pain studies with decreased binding in several key areas involved in pain perception. The dopaminergic pathways have also been implicated in pain processing in animal and patient studies. Early studies in fibromyalgia patients indicate reduced presynaptic dopaminergic activity in several brain regions in which dopamine plays a critical role in modulating nociceptive processes. Similar to the endogenous opioid system, the issue of cause and effect between a “functional hypodopaminergic state” and pain has yet to be resolved, making this an exciting area of current research.

Conclusion

Knowledge regarding how pain is perceived at a central level in humans is growing. An extensive network is recruited that is highly modifiable depending upon genetics, the environment, mood and the particular injury sustained. Combined, these produce a unique cerebral signature that produces an individualized pain experience.

References

1. Tracey I, Mantyh PW (2007) The cerebral signature for pain perception and its modulation. *Neuron* 55:377–391
2. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK (2005) Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 9:463–484
3. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D (2003) COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 299:1240–1243
4. Fields H (2005) Central nervous system mechanisms of pain modulation. In: Wall PM, R, (ed) *Textbook of pain*. Churchill Livingstone, London, 125–142
5. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004) Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303:1162–1167
6. Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R, Matthews PM, Rawlins JN, Tracey I (2001) Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci* 21:9896–9903
7. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ (2004) Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 127:835–843
8. Lorenz J, Minoshima S, Casey KL (2003) Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain* 126:1079–1091
9. Suzuki R, Rygh LJ, Dickenson AH (2004) Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci* 25:613–617
10. Zambreanu L, Wise RG, Brooks JC, Iannetti GD, Tracey I (2005) A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. *Pain* 114:397–407

Pain in Children

PATRICIA A. McGRATH^{1,2}, TRICIA WILLIAMS¹

¹Department of Anaesthesia, Divisional Centre of Pain Management and Research, The Hospital for Sick Children, Toronto, ON, Canada

²Neuroscience and Mental Health Program, Research Institute at The Hospital for Sick Children; Department of Anaesthesia, The University of Toronto, Toronto, ON, Canada

Synonyms

Pediatric pain; Adolescent pain

Definition

The unique aspects of nociceptive processing and pain perception associated with a developing pain system and a maturing child, in contrast to those of a mature adult.

Children are not “little adults” with respect to nociceptive processing and pain perception. The ▶[developing nociceptive system](#) responds differently to injury (i.e., increased excitability and sensitization) when compared to the mature adult system [1,2]. Moreover, a child’s pain appears to have a greater degree of ▶[plasticity](#) when compared to that of adults – more influenced by cognitive, behavioral, and emotional factors [3].

Characteristics

Children’s Pain Problems

Like adults, children can experience many different types of pain throughout their lives – acute pain due to disease or trauma, recurrent episodes of headache, stomach ache, or limb pain unrelated to disease, and chronic pain due to injury, disease, psychological factors, or of unknown etiology. However, the prevalence of certain types of pain is different for adults and children. For example, chronic back pain is a major problem for adults but not for children. Recurrent pain syndromes (i.e., abdominal, headache, limb pains or “growing pains”) are more common pain problems for children.

Pain prevalence increases with age and certain pain conditions vary with sex and age. For example, clinical referrals indicate that Complex Regional Pain Syndrome-Type 1 affects girls more than boys with a ratio of ~6–9:1 and affects children primarily in their pre- and early teen years. Complex idiopathic pain conditions and somatization disorders seem to predominantly affect older adolescents.

Although we lack precise data on the incidence and prevalence of many childhood pain conditions, an increasing number of epidemiological studies are focused on obtaining such data, identifying individual risk and prognostic factors and documenting the long term impact for children and their families.

Developmental Considerations

Considerable neuronal plasticity is evident throughout the developing system from the periphery to the brain (for review, [1,2]) (see ▶[Development of nociception](#)). Although basic nociceptive connections are formed before birth, these systems are immature and exhibit increased responsivity in comparison to the adult animal. The conduction velocity of afferent fibers, action potential shape, receptor transduction, firing frequencies and receptive field properties change substantially over the postnatal period. High threshold Aδ mechanoreceptors (which respond maximally to noxious mechanical stimuli) and low threshold Aβ mechanoreceptors (which respond maximally to innocuous stimuli) respond with lower firing frequencies than those in the adult animal. The receptive fields of dorsal horn cells are larger in the newborn. The larger receptive fields and dominant A-fiber input increases

the likelihood of central cells being excited by peripheral sensory stimulation and acts to increase the sensitivity of infant sensory reflexes. Some inhibitory mechanisms (**►Inhibitory mechanisms in developing system**) in the dorsal horn are immature at birth and descending inhibition is delayed. The lack of descending inhibition in the neonatal dorsal horn means that an important endogenous analgesic system that should attenuate noxious input as it enters the spinal cord is lacking, and thus the effects of the input may be more profound than in the adult [2].

Most studies in developmental neurobiology have been conducted on rat pups because they have comparable developmental timetables with respect to the anatomy, chemistry, and physiology of maturing human pain pathways. To study neural function in human infants, investigators have monitored behavioral and neurophysiologic responses, and revealed comparable findings of plasticity and increased excitability in the developing nervous system (for review, [1,4]). In comparison to adults, young infants have exaggerated reflex responses (i.e., lower thresholds and longer lasting muscle contractions) in response to certain types of trauma, such as needle insertion. Repeated mechanical stimulation at strong (but not pain-producing) intensities can cause sensitization in very young infants, while repeated painful procedures such as those required during intensive care can profoundly affect sensory processing in infants. Infants after surgery can develop a striking hypersensitivity to touch, as well as to pain.

While we do not know specifically how such injuries may affect the mature human pain system or influence adult pain perception, increasing attention is focused on the possible consequences of untreated pain, particularly in infants [5]. For example, circumcised newborn infants display a stronger pain response to subsequent routine immunizations at 4 and 6 months than uncircumcised infants, but application of lidocaine-prilocaine anesthetic cream at circumcision attenuates the pain response to the subsequent immunizations [6]. Studies of former premature infants who required intensive care have shown behavioral differences related to early pain experiences. The results of behavioral studies in infants, like those from neurobiological studies in animals, indicate increased responsivity to pain.

Factors that Modify Children's Pain

A child's pain perception can be regarded as plastic from a psychological, as well as biological perspective. Tissue damage initiates a sequence of neural events that may lead to pain, but many developmental, social, and psychological factors can intervene to alter the sequence of nociceptive transmission and thereby modify a child's pain. Child characteristics, such as cognitive level, sex, gender, temperament, previous pain experience, family, and cultural background shape

generally how children interpret and cope with pain (for review [7–9]).

In contrast, **►situational factors** vary dynamically, depending on the specific circumstances in which a child experiences pain. For example, a child receiving treatment for cancer may have repeated injections, central venous port access and lumbar punctures – all of which can cause pain (depending on the analgesics, anesthetics, or sedatives used). Even though the tissue damage from these procedures is the same each time, the particular set of situational factors for each treatment is unique for a child. The expectations, behaviors and emotional state of the child, parent and health care provider all play a critical role. “What children and parents understand, what they (and health care staff) do, and how children and parents feel” can profoundly impact a child's pain experience. Certain situational factors can intensify pain and distress, while others can eventually trigger pain episodes, prolong pain related disability, or maintain the cycle of repeated pain episodes in recurrent pain syndrome [3]. Parents and health care providers can dramatically improve a child's pain experience and minimize their disability by modifying children's understanding of a situation, their focus of attention, perceived control, expectations for obtaining eventual recovery and pain relief, and the meaning or relevance of the pain.

Situational factors may affect children even more than adults. Adults typically have experienced a wide variety of pains (i.e., diverse etiology, intensity and quality), providing them with a broad base of knowledge and coping behaviors. When adults encounter new pains, they evaluate them primarily from the context of their cumulative life experience. In contrast, children with more limited pain experience must evaluate new pains primarily from the context of the immediate circumstances. Children's understanding of pain, pain coping strategies, and the impact of pain increase with age, but many questions remain about the interplay of maturation, cognitive development, and experience in mediating a child's pain.

Pain Measures for Infants and Children

Pain assessment is an intrinsic component of pain management in infants and children. Clinicians need an objective measure of pain intensity and an understanding of the factors that cause or exacerbate pain for an individual child. More than 60 pain measures are now available for infants, children, and adolescents (for review, [10]). While no single pain measure is appropriate for all children and for all situations in which they experience pain, we should be able to evaluate pain for almost every child.

►Physiological parameters including heart rate, respiration rate, blood pressure, palmar sweating, blood cortisol and cortisone content, O₂ levels, vagal tone and

endorphin concentrations have been studied as potential pain measures. However, they reflect a complex and generalized stress response, rather than correlate with a particular pain level. As such, they may have more relevance as distress indices within a broader behavioral pain scale. Behavioral scales record the type and amount of pain-related behaviors children exhibit. Since a child's specific pain behaviors depend on the type of pain experienced, different scales are usually required for acute and persistent pain. Clinicians monitor children for a specified time period and then complete a checklist noting which distress behaviors (e.g., crying, grimacing, guarding) occur. Behavioral scales must be used for infants and children who are unable to communicate verbally. Recently, investigators are validating pain scales for children who are ►**developmentally disabled**. However, the resulting pain scores are indirect estimates of pain and do not always correlate with children's own pain ratings. Even though clinicians may use diaries rather than formal scales, prospective evaluation of a child's behavior is an essential component of pain management, providing information about medication use, compliance with treatment recommendations, and the extent of pain-related disability (i.e., school attendance, physical activities, and social activities with peers).

Psychological or self-report measures include a broad spectrum of projective techniques, interviews, questionnaires, qualitative descriptive scales, and quantitative rating scales designed to capture the subjective experience of a child's pain [11]. By the age of five, most children can differentiate a wide range of pain intensities, and many can use simple ratio and interval pain scales (e.g., visual analog scales, numerical scales, faces, verbal descriptor scales) to rate their pain intensity. Many scales have excellent psychometric properties, are convenient to administer, easy for children to understand, adaptable to many clinical situations, and help parents to monitor their child's pain at home. Interviews, usually conducted independently with a child and parents, are the cornerstone of assessment for children with persistent pain, enabling clinicians to identify relevant child, family, and situational factors that contribute to children's pain and disability problems.

Child-centered Pain Management

Pain control is not merely "drug versus nondrug therapy," but rather an integrated approach to reduce or block nociceptive activity by attenuating responses in peripheral afferents and central pathways, activating endogenous pain inhibitory systems, and modifying situational factors that exacerbate pain. Adequate analgesic prescriptions, administered at regular dosing intervals, must be complemented by a practical cognitive-behavioral approach to ensure optimal pain relief. Pain control is achieved practically by adjusting

both drug and nondrug therapies in a rational child-oriented manner based on the assessment process [12]. Analgesics include acetaminophen, non-steroidal anti-inflammatory drugs, and opioids. ►**Adjuvant analgesics** include a variety of drugs with analgesic properties, such as anticonvulsants and antidepressants that were initially developed to treat other health problems, but whose therapeutic uses have been expanded. The use of adjuvant analgesics has become a cornerstone of pain control for children with chronic pain, especially when pain has a neuropathic component. Children with severe pain may require progressively greater and more frequent opioid doses due to drug tolerance and should receive the doses they need to relieve their pain. The fear of opioid addiction in children has been greatly exaggerated. Neonates and infants require the same three categories of analgesic drugs as older children. However, premature and term newborns show reduced clearance of most opioids. The differences in pharmacokinetics and pharmacodynamics among neonates, preterm infants, and full-term infants, warrant special dosing considerations for infants and close monitoring when they receive opioids.

An extensive array of nondrug therapies is available to treat a child's pain including physical, psychological and complementary and alternative approaches. Counseling, attention and distraction, guided imagery, hypnosis, relaxation training, biofeedback, and behavioral management are used routinely to treat a child's procedural pain and chronic pain. Children seem more adept than adults at using psychological therapies, presumably because they are generally less biased than adults about their potential efficacy. Strong and consistent scientific evidence supports the efficacy of many psychological therapies for relieving children's procedural pain and for relieving childhood headache, but few rigorous evaluations have been conducted on their efficacy for relieving other types of chronic pain – even though they are considered an essential component of many treatment programs.

Clinical and Research Challenges

As a result of extensive research, we have gained better insights about how the developing nociceptive system responds to tissue injury, how children perceive pain, how to assess pain in infants and children, and which drug and nondrug therapies will alleviate their pain. The emphasis has shifted gradually from an almost exclusive disease-centered focus – detecting and treating the putative source of tissue damage – to a more child-centered perspective, assessing the child with pain, identifying contributing psychological and contextual factors, and then targeting interventions accordingly. However, serious challenges remain from both research and clinical perspectives [13].

We have discovered much about the plasticity of the developing nociceptive system, but still have much to

learn about how signals from painful stimuli are processed, especially at higher levels (see ►[Pain imaging](#)). Although we need further developmental research in neurobiology, neurophysiology, and pharmacology, we now know that infants seem particularly vulnerable because of their heightened responsivity to tissue injury and we must devote particular attention to their pain management.

We need to apply the existing knowledge about pain assessment and pain management more consistently within our clinical practice. Regrettably, many hospitals still do not require consistent documentation of children's pain, preventing us from ensuring that children's pain is adequately controlled. Hospital administrators or accreditation organizations should establish children's pain control as a priority. In spite of established analgesic dosing guidelines for infants and children, the undertreatment of postoperative and chronic pain is a continuing problem in many centers.

Moreover, increasing responsibility for evidence-based practice dictates that health care providers adopt clear guidelines for determining when treatments are effective and for identifying children for whom they are most effective. We lack data from well-designed cohort studies and randomized controlled trials to validate the efficacy of many interventions (both drug and nondrug therapies) used extensively in clinical practice. Although cognitive-behavioral interventions are critical components of pain management programs for chronic pain, most of the data supporting their efficacy is derived from studies of childhood headache [14].

We critically need data on child-centered treatment efficacy—that is, when interventions are selected for the individual child with pain, based on an assessment of the specific cognitive, behavioral, and emotional factors contributing to their pain and disability. We need longitudinal studies to identify key risk factors that influence a child's vulnerability to chronic pain, in particular the apparent increased vulnerability in females. Future studies should use brain imaging technology and psychophysical measurement to evaluate the neural mechanisms underlying chronic pain and cognitive function in children. Our ultimate and continuing challenges are to better understand the experience of children's pain and to improve clinical practice, so that health care providers use the existing “state of the art” pain scales, interpret children's pain scores to guide therapeutic decisions, and document treatment effectiveness.

References

1. Andrews Campbell K (2007) Infant Pain Mechanisms. In: Schmidt RF, Willis WD (eds) *Encyclopedic reference of pain*. Springer-Verlag, New York, pp 976–981
2. Fitzgerald M, Howard RF (2003) The neurobiologic basis of pediatric pain. In: Schechter NL, Berde CB, Yaster M (eds) *Pain in infants, children, and adolescents*, 2nd edn. Lippincott Williams and Wilkins, Baltimore, pp 19–42
3. McGrath PA, Dade LA (2004) Effective strategies to decrease pain and minimize disability. In: Price DD, Bushnell MC (eds) *Psychological modulation of pain: integrating basic science and clinical perspectives*. IASP Press, Seattle, pp 73–96
4. Johnston C, Stevens B, Boyer K et al. (2003) Development of psychologic responses to pain and assessment of pain in infants and toddlers. In: Schechter NL, Berde CB, Yaster M (eds) *Pain in infants, children, and adolescents*, 2nd edn. Lippincott Williams and Wilkins, Baltimore, pp 105–127
5. Grunau RE (2000) Long-term consequences of pain in human neonates. In: Anand KLS, Stevens BJ, McGrath PJ (eds) *Pain in neonates*, 2nd edn. Elsevier, Amsterdam, pp 55–76
6. Taddio A, Katz J, Ilersich AL et al. (1997) Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 349:599–603
7. Schechter NL, Berde CB, Yaster M (eds) (2003) *Pain in infants, children, and adolescents*. Lippincott Williams and Wilkins, Baltimore
8. McGrath PJ, Finley GA (eds) (2003) *Pediatric pain: biological and social context*. IASP Press, Seattle
9. Unruh AM, Campbell MA (1999) Gender variations in children's pain experiences. In: Finley GA, McGrath PJ (eds) *Chronic and recurrent pain in children and adolescents*. IASP Press, Seattle, pp 199–241
10. McGrath PA (2007) Pain assessment: children. In: Schmidt RF, Willis WD (eds) *Encyclopedic reference of pain*. Springer-Verlag, New York, pp 1644–1648
11. Champion GD, Goodenough B, von Baeyer CL et al. (1998) Measurement of pain by self-report. In: Finley GA, McGrath PA (eds) *Measurement of pain in infants and children*. IASP Press, Seattle, pp 123–160
12. Brown SC (2007) Analgesic guidelines for infants and children. In: Schmidt RF, Willis WD (eds) *Encyclopedic reference of pain*. Springer-Verlag, New York, pp 78–83
13. McGrath PA (2007) Pain in children. In: Schmidt RF, Willis WD (eds) *Encyclopedic reference of pain*. Springer-Verlag, New York, pp 1665–1669
14. Eccleston C, Morley S, Williams A et al. (2002) Systematic review of randomised controlled trials of psychological therapy for chronic pain in children and adolescents, with a subset meta-analysis of pain relief. *Pain* 99:157–165

Pain in Older Adults (Including Older Adults with Dementia)

THOMAS HADJISTAVROPOULOS

Centre on Aging and Health and Department of Psychology, University of Regina, Regina, SK, Canada

Synonyms

Pain in the elderly; Pain among seniors; Pain in patients with dementia

Definition

Most investigations focusing on pain among older adults (elderly persons) involve participants who are at least 60 or 65 years of age.

Characteristics

Prevalence

Although the prevalence of acute pain remains steady across the lifespan, there is an increased prevalence of chronic pain at least until the seventh decade of life [1]. Limited evidence also suggests a plateau or even a slight reduction in the frequency of pain complaints after age 80 [1].

Pain is a very common problem among older adults. Chronic pain affects at least 50% of seniors living in the community and approximately 80% of residents of long-term care facilities. Moreover, in a large scale Canadian investigation of nursing home residents, it was shown that conditions likely to cause pain occur with equal frequency in residents with and without dementia [2]. Despite the increasing prevalence of most pain problems with age, the study of pain among older adults had not received much literature attention until recently [1].

Pain Perception, Thresholds and Tolerance

Age-related changes in peripheral, spinal and central nervous system [▶nociceptive pathways](#) would be expected to alter pain sensitivity and therefore the perception of noxious stimulation [3]. Indeed, evidence suggests that age can have an impact on the function of nociceptive pathways and mechanisms, including alterations in afferent transmission and descending modulation [1]. More specifically, for example, research on the perceptual experience that tends to accompany activations of nociceptive fibers has suggested the presence of a selective age-related impairment in A-fiber function and a greater reliance on C-fiber information in older adults. Considering that A-fibers subserve the epicritic, first warning aspects of pain, while C-fiber information is more diffuse, dull and prolonged, it might be reasonable to expect some changes in pain intensity and quality among elderly persons [3].

Research has also revealed evidence that temporal summation (i.e., the enhancement of pain sensation that is associated with repeated stimulation) is altered in older adults. Temporal summation is the result of transient, repetitive activation of dorsal horn neurons in the spinal cord and is believed to play a central role in the development of [▶hyperalgesia](#) and post-injury tenderness [3]. Based on the findings that are available in the literature, it is likely that post-injury tenderness and hyperalgesia may take longer to resolve among older adults [3]. An additional age-related change has been demonstrated by Washington, Gibson and Helme [4], who have shown that endogenous inhibitory pain control mechanisms that descend from the cortex and

midbrain onto spinal cord neurons decline with advancing age. Such a decline could be expected to reduce the ability of older adults to cope with persistent pain states [3].

With respect to neurochemical and morphological age-related changes in the central nervous system, Gibson, Gorman and Helme [5] used the pain-related encephalographic response to index the central nervous system processing of noxious stimulation. These researchers found that older adults tended to display a significant reduction in peak amplitude and an increase in response latency. They concluded that these findings were suggestive of a reduced cortical activation and slowing in the cognitive processing of noxious information. Nonetheless, it is important to remember that despite such limited laboratory evidence of reduced sensitivity to pain with advancing age, there is no evidence to suggest that seniors who report pain suffer any less than their younger counterparts [1].

Research has also examined the possible impact of dementia on pain responses. In general, the findings have shown no difference in the [▶pain threshold](#) of those with mild to moderate Alzheimer's disease, despite an increase in [▶pain tolerance](#) when compared to age matched controls [6,7]. Nonetheless, Benedetti et al. [6] have demonstrated that whereas the sensory-discriminative components of pain are preserved even in advanced stages of Alzheimer's disease, the cognitive and affective functions, which are related to both anticipation and autonomic reactivity, are severely affected. This sensory-affective dissociation is well correlated with neuropathological findings in Alzheimer's disease. Moreover, Benedetti et al. [6,7] showed that pain tolerance among older adults with Alzheimer's disease is tightly related to the severity of the disease. That is, more severe cognitive impairment and more significant electroencephalogram (EEG) changes were associated with higher pain tolerance. Thus, despite the preservation of pain thresholds in the presence of dementia, there is an increase in pain tolerance with increased severity of the disease. It is noted, however, that clinical research has shown that the reflexive reactions that dementia patients show to painful stimulation (e.g., pain due to discomforting physiotherapy exercises) are comparable or more intense than the reactions of cognitively intact patients [8]. Such clinical findings underscore the importance of managing pain effectively regardless of patient cognitive status.

Age Differences in Psychosocial Aspects of Pain

There is evidence of psychosocial differences in the mediators and context of pain. Although not perfectly consistent across studies, the evidence shows age-related differences in beliefs and attributions about pain as well as coping strategies [9]. There is, for

example, evidence of increased stoicism among older adults when it comes to the reporting of symptoms. This stoicism could lead to an underreporting of pain among older adults [9]. Moreover, the social context and stressors that affect seniors with pain differ from those of younger persons. For example, younger adults with chronic pain conditions are often concerned about issues relating to return to work whereas older persons are often retired, may be widowed and may be more concerned about loneliness and possible social isolation.

The Assessment of Pain in the Older Adult

Given age-related differences in the social context and co-morbidities of chronic pain, research has focused increasingly on the validation of pain assessment tools among older adults [10]. Instruments that are specialized in the assessment of the older adult have also been developed [10].

The accurate assessment of pain in the older adult is especially challenging when it comes to persons with severe dementia who have limited ability to communicate. Because pain is a subjective phenomenon, clinicians tend to rely on self-report. Recently, there have been worthwhile efforts to develop and validate observational measures of pain that rely on the recording of pain-related behaviors such as facial expressions and paralinguistic vocalizations (such assessment tools have been reviewed elsewhere [8]).

The Treatment of Pain in the Older Adult

Although the prevalence of chronic pain increases with age, pain is always the result of pathology and is never a natural part of being old. As such, it is always important to manage chronic pain. Recommended doses of drugs used for pain management in older adults are often lower than doses used in younger persons because of age-related physiological changes (e.g., age-related changes in fat to muscle ratio, slowing of metabolic rates, lower protein levels in the blood). Although numerous drugs have been shown to be effective in treating pain in older adults, more research concerning the ►pharmacokinetics, ►pharmacodynamics, efficacy and safety of medications in older persons is needed [9]. In addition, many of the painful conditions that elderly persons tend to suffer are responsive to physiotherapy, although special adaptations may be required for frail seniors [9]. Finally, initial evidence suggests that ►cognitive behavior therapy can be helpful in assisting older adults with pain management [9].

References

1. Charlton JE (ed) (2005) Core curriculum for professional education in pain, 3rd edn. IASP Press, Seattle
2. Proctor W, Hirdes J (2001) Pain and cognitive status among nursing home residents in Canada. *Pain Res Manag* 6:191–205
3. Gibson SJ, Chambers C (2004) Pain over the life span, in *Pain: Psychological perspectives*. In: Hadjistavropoulos T, Craig KD (eds) Lawrence Erlbaum Associates, Mahwah, NJ
4. Washington LL, Gibson SJ, Helme RD (2000) Age-related differences in endogenous analgesic response to repeated cold water immersion in human volunteers. *Pain* 89:89–96
5. Gibson SJ, Gorman MM, Helme RD (1990) Assessment of pain in the elderly using event-related cerebral potentials. In: Bond MR, Charlton JE, Woolf C (eds) *Proceedings of the VIth World Congress on Pain*, Elsevier, Amsterdam
6. Benedetti F et al. (2004) Pain reactivity in Alzheimer patients with different degrees of cognitive impairment and brain electrical activity deterioration. *Pain* 111 (1–2):22–29
7. Benedetti F et al. (1999) Pain threshold and tolerance in Alzheimer's disease. *Pain* 80(1–2):377–382
8. Hadjistavropoulos T (2005) Assessing pain in older persons with severe limitations in ability to communicate. In: Gibson SJ, Weiner DK (eds) *Pain in older persons*. IASP Press, Seattle
9. Gibson SJ, Weiner DK (eds) (2005) *Pain in older persons*. IASP Press, Seattle
10. Herr KA (2005) Pain assessment in the older adult with verbal communication skills. In: Gibson SJ, Weiner DK (eds) *Pain in older persons*. IASP Press, Seattle, pp 111–133

Pain in Patients with Dementia

►Pain in Older Adults (Including Older Adults with Dementia)

Pain in the Elderly

►Pain in Older Adults (Including Older Adults with Dementia)

Pain in the Head

►Headache

Pain Modulation

► Descending Modulation of Nociception

Pain Psychophysics

JOEL D. GREENSPAN

Department of Biomedical Sciences, University of Maryland Dental School, Baltimore, MD, USA

Synonyms

Quantitative sensory testing QST

Definition

The systematic evaluation of the quantitative relationship between physical stimuli and the pain they evoke.

Characteristics

The discipline of ►psychophysics was developed in the German experimental psychology laboratories of the early nineteenth Century. It has been applied to every sensory system, including pain. The earliest published work in pain psychophysics recognized today is that of Ernst Weber [1]. While most of Weber's work in psychophysics addresses tactile perception, a portion encompasses pain. The first major opus in pain psychophysics of the twentieth Century was that of James Hardy and colleagues at Cornell University. Over 200 papers from this group were distilled for the book "Pain sensations and reactions" [2]. This body of work was a principal reference for pain psychophysics for decades, despite a reliance on a narrow range of approaches that were not always found to generalize in subsequent studies.

The two essential components for psychophysical evaluation of any sensory system are (i) controlled stimuli and (ii) a valid method of quantifying sensory experience. For pain psychophysics, the development of reliable pain-evoking stimuli was complicated by the need to avoid tissue damage. The most commonly used stimulation techniques are cutaneous heating and mechanical pressure applied to cutaneous and/or deeper tissues. However, several other forms of stimulation are used for pain psychophysics, including cold, electrical, chemical, laser, and visceral distention [3].

Pain Threshold

One principal psychophysical measure is ►threshold. Simply stated, threshold is the minimal level of

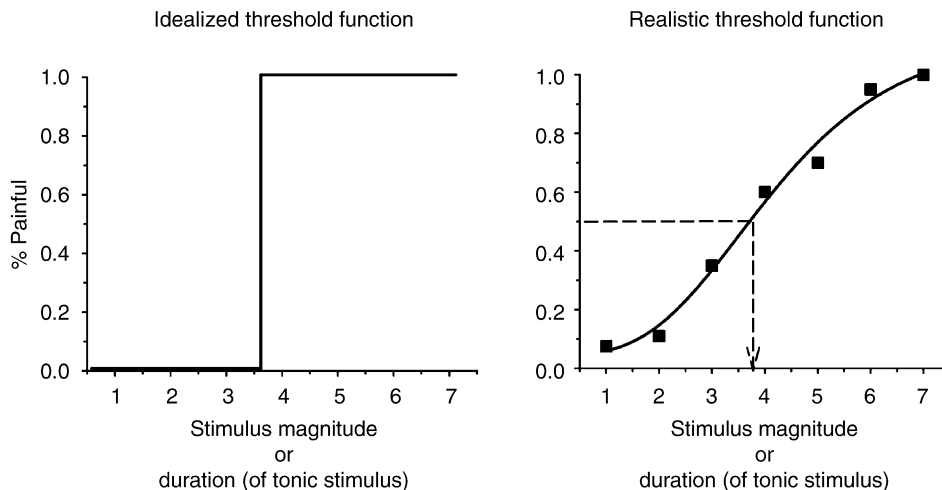
stimulation needed to evoke a sensation. By extension pain threshold is the minimal level of stimulation needed to evoke a sensation of pain. Accordingly, thresholds are reported in terms of stimulus values, such as temperature (in °C) or mechanical forces (kg equivalent weight, or Newtons). An alternative measure is the time it takes a constant, sustained stimulus to be perceived as painful, thus measuring pain threshold in terms of seconds.

The assessment of pain threshold is more complicated than other sensory thresholds because of the nature of pain and people's concept of it. In other sensory modalities, threshold is recognized by the "step" between no sensation and sensation. Thus, the subject is attempting to distinguish between sensing nothing and something. For pain thresholds, the subject is instead distinguishing between two types of sensation – one considered painful and one non-painful. Thus, a critical element in pain threshold determination is the particular sensory experience an individual considers painful. This factor will be influenced by, among other things, the subject's pain experience history, and the instructions given by the experimenter. For instance, thresholds are likely to be different if a subject is instructed to indicate when he perceives "pain" versus when he perceives "a sharp or burning sensation" or "an uncomfortable sensation." It is also possible that a subject's criterion for judging what sensation is painful changes in the course of an evaluation session. Furthermore, the likelihood and extent of such changes can vary depending upon the range and number of stimuli applied [4]. Several other factors can influence pain threshold values, including features of the psychophysical protocol (e.g., the specific design, stimulus parameters, the range of stimuli, the threshold calculation procedure), which makes it questionable to compare threshold values across studies that vary with respect to these and any other protocol features.

Another important fact to recognize is that threshold is a statistical entity. While we are accustomed to representing thresholds as very precise values (i.e., heat pain thresholds expressed as temperature at a 0.1°C level of precision), it is not the case that weaker stimuli are necessarily painless, and stronger ones are always painful. Instead, there is a range of stimuli for which the lower values are less frequently painful and the higher values are more frequently painful. The threshold value, in principle, is the midpoint of that range (Fig. 1).

This concept applies whether one is considering data derived from a single person tested repeatedly, or from a group of people.

Heat pain threshold has been found to be fairly consistent across many body sites. However, heat pain thresholds are significantly higher on ►glabrous skin than on hairy skin of the extremities. This relative consistency across the body allows one to assess regional pain threshold abnormalities by comparing



Pain Psychophysics. Figure 1 Ideally, pain threshold can be envisioned as the stimulus intensity that divides non-painful from painful intensities of stimulation (*left*). But, in reality, there is a range of stimulus intensities that are sometimes perceived as painful and sometimes as non-painful. Thus, pain threshold is typically regarded as the stimulus intensity that is painful 50% of the time (*right*).

thresholds between two body sites, when one of them is accepted as a reference. This approach is often done by comparing thresholds between homolateral body sites in the cases of unilateral sensory abnormalities [5]. Despite this intra-personal consistency, there is considerable inter-personal variability in pain threshold. This feature has been demonstrated in studies that have evaluated a large number of subjects in attempts to develop a normative database of pain thresholds [6].

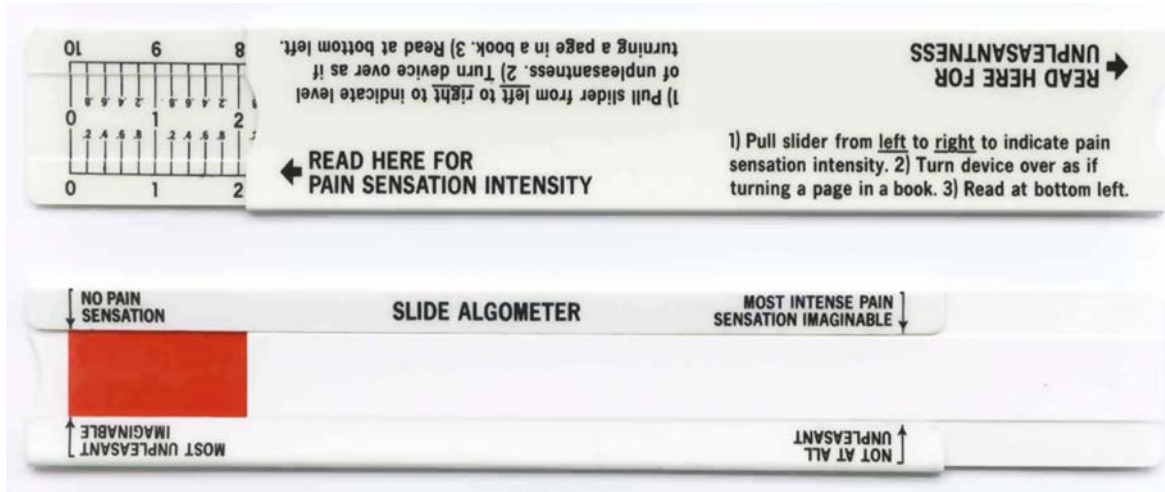
While the concept of psychophysical threshold has been used for almost two centuries, it has been criticized as a strict measure of sensory perception because it can be influenced by psychological states such as expectancy and anticipated rewards. In an attempt to account for these and other “non-sensory” factors that could influence threshold determination, the approach of ►[signal detection theory](#) (SDT) was adapted for psychophysics [7]. This approach allowed for the distinction between stimulus discriminability (d') and response bias (β), in which the former was the “bias-free” measure of sensory detection. Threshold measures cannot make this distinction. Approaches based on SDT have been applied to pain psychophysics; however, problems particular to pain psychophysics have been noted. Despite the advantage of SDT approaches in distinguishing stimulus discriminability from response bias in psychophysical assessments, the major drawback of this approach is the need for many more stimulus trials than are needed for most threshold protocols. In addition, SDT assumes a perceptual stability over the course of testing, which is not necessarily the case for pain. Another concern is that knowing how discriminable two

(or more) stimuli are from one another is not the same information as how painful those stimuli are. Thus, the kind of information derived from STD-derived protocols are supplemental to, rather than replacements for, the type of information gathered using other psychophysical approaches to pain perception.

Suprathreshold Pain Scaling

Another major psychophysical endpoint is evaluation of perception above threshold (suprathreshold perception). The principle is to have the subject represent the sensory experience on a quantitative continuum – often referred to as “scaling” perception. There are many ways to accomplish this, and protocols are based on either direct or indirect methods. Indirect scaling methods require the subject to use another continuum to match the perception under investigation. An example of this is to have the subject adjust the volume of a sound so that the loudness matches the intensity of another sensory dimension, such as pain. In this way, the pain intensity can be measured in terms of decibels of sound. Another approach is to have the subject draw a line length to represent the intensity of a sensation, allowing the sensation intensity to be measured in millimeters.

The direct scaling methods require the subject to choose a number that reflects perceptual intensity, and thus do not require an intermediate modality such as another sensory dimension or a motor task. These direct scaling methods have been more frequently employed for pain psychophysics over the last few decades. In most pain studies, subjects are provided a number



Pain Psychophysics. Figure 2 A mechanical visual analog scale for pain rating developed by Dr. Donald D. Price and colleagues. *Bottom:* A sliding plastic piece moves to reveal a red bar. The subject adjusts the length of the red bar to match the perceived pain intensity (in the orientation shown), or the perceived unpleasantness (when rotated 180°). *Top:* The number at the edge of the adjusted plastic piece is the numerical value assigned either pain intensity or unpleasantness. Figure courtesy of Dr. Price.

Pain intensity scale		Unpleasantness scale	
20		20	
19		19	
18	Extremely intense	18	
17	Very intense	17	Very intolerable
16	Intense	16	
15		15	Intolerable
14	Strong	14	
13	Slightly intense	13	Very distressing Slightly intolerable
12	Barely strong	12	Very annoying
11	Moderate	11	Distressing
10		10	Very unpleasant
9		9	Slightly distressing
8	Mild	8	Annoying
7		7	Unpleasant
6	Very mild	6	Slightly annoying
5	Weak	5	Slightly unpleasant
4	Very weak	4	
3		3	
2		2	
1	Faint	1	
0	No pain sensation	0	Neutral

Gracely box SL

Gracely box SL

Pain Psychophysics. Figure 3 Pain rating scales with descriptors developed by Dr. Richard H. Gracely and colleagues. The subject reports the perceived pain intensity (a) or unpleasantness (b) by choosing a number between 0 and 20. Placement of descriptors along the length of the numeric scale, which serve to provide connotative meaning to the numbers, was based on psychometric procedures described in [9]. Figure courtesy of Dr. Gracely.

scale to use, which can be as limited as 0–5, or as large as 0–100, or even unbounded. In many instances, the numeric scale also includes descriptors at specific points to give the numeric scale a qualitative frame of reference. One of the most commonly used scales for pain ratings is a 0–100 visual analog scale (VAS) with descriptors at both ends of the scale (Fig. 2).

This scale has been validated and found to produce data with ratio scale properties suitable for parametric analysis [8]. Other pain scales have been developed with more descriptors, based on psychometrically determined associations among the descriptors (Fig. 3a) [9,10].

The principle of assigning descriptors along a numeric scale for the subject can be an advantage, but also potentially problematic. On one hand, descriptive anchors serve to give the numbers a consistent connotative meaning to the subjects, and thereby help to standardize the scale. On the other hand, if different people interpret the same term differently (Is your concept of “extremely intense” the same as mine?), the presence of these terms can introduce an idiosyncratic bias, rather than standardizing the numeric scale. Despite this possibility, and the inherent uncertainty of measuring a subjective phenomenon, these types of scales have been successfully used for many psychophysical studies of pain over the last few decades.

While the aforementioned scales are designed to measure pain intensity, a similar set of scales have been developed to measure pain affect or unpleasantness (Figs. 2 and 3b). In principle, any perceptual dimension could be measured with a similarly constructed scale.

Pain Tolerance

Pain tolerance is less frequently used than pain threshold in scientific studies, and it has some significant disadvantages: (i) For some forms of stimulation, pain tolerance cannot be reached without risking tissue injury; (ii) Pain tolerance generally shows greater variability than threshold, both within and across subjects; (iii) It is more widely altered by subject bias or past experience than threshold. However, pain tolerance measures a qualitatively different aspect of the pain experience than does pain threshold. Arguably, pain tolerance is a measure more reflective of the affective and motivational aspects of the pain experience, while threshold is a measure of the discriminative aspect. One common form of this test is the “▶cold pressor test,” which involves submersion of a body part in ice water. Another test involves ischemic pain, produced by applying a pressure cuff on the subject’s arm.

References

1. Ross HE, Murray DJ (eds) (1978) *The sense of touch* (transl. Weber EH). Academic Press, New York

2. Hardy JD, Wolff HG, Goodell H (1952) *Pain sensations and reactions*. Williams and Wilkins, Baltimore
3. Graven-Nielsen T, Sergerdahl M, Svensson P, Arendt-Nielsen L (2001) Methods for induction and assessment of pain in humans with clinical and pharmacological examples. In: Kruger L (ed) *Methods in pain research*. CRC Press, Boca Raton, FL, pp 263–304
4. Gracely RH, Naliboff BD (1996) Measurement of pain sensation. In: Kruger L (ed) *Pain and touch*. Academic Press, San Diego, CA, pp 243–313
5. Greenspan JD, Ohara S, Sarlani E, Lenz FA (2004) Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. *Pain* 109:357–366
6. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC (2006) quantitative sensory testing in the German research network on neuropathic pain (DFNS): standardized protocol and reference values. *Pain* 123:231–243
7. Green DM, Swets JA (1966) *Signal detection theory and psychophysics*. Robert E. Krieger, Huntington, NY
8. Price DD, McGrath PA, Rafii A, Buckingham B (1983) The validation of visual analogue scales as ratio scales measures for chronic and experimental pain. *Pain* 17:45–56
9. Gracely RH, McGrath P, Dubner R (1978) Ratio scales of sensory and affective verbal pain descriptors. *Pain* 5:5–18
10. Greenspan JD, Roy EA, Caldwell PA, Farooq N (2003) Thermosensory intensity and affect throughout the perceptible range. *Somatosens Mot Res* 20:19–26

Pain System

▶Ascending Nociceptive Pathways

Pain Threshold

Definition

The International Association for the Study of Pain defines pain threshold as the least amount of pain that a person can recognize.

▶Pain in Older Adults (Including Older Adults with Dementia)

Pain Tolerance Level

Definition

The International Association for the Study of Pain defines pain tolerance level as the greatest amount of pain that a person can tolerate.

► Pain in Older Adults (Including Older Adults with Dementia)

Pain Unpleasantness

Definition

The immediate, disagreeable aspect of pain, similar to feelings of thermal distress (too hot or cold), thirst, or hunger, that motivates behaviors to reduce this feeling state. This immediate state is in contrast to the emotional reactions and feeling states associated with thoughts about pain (pain emotion), such as anxiety, depression, fear, and despair. In the case of injury, the unpleasantness of pain usually motivates movements to escape or to minimize the injury (pain evoked movement). After the injury, during the healing phase, the unpleasantness of pain may inhibit movement to protect the injured area and promote healing (movement evoked pain).

► Emotional/Affective Aspects of Pain

Painful Neuropathies

► Voltage-gated Sodium Channels: Multiple Roles in the Pathophysiology of Pain

Palaeocerebellum

Synonyms

► Paleocerebellum

Definition

Phylogenetically, a very old part of the cerebellum. Corresponds to the vermis cerebelli with its surrounding intermediate part (paravermal part). The afferents of this region come from the spinal cord, hence this part is also called the spinocerebellum.

► Cerebellum

Palaeomagnetism

Definition

The study of remanent magnetization of rocks and sediments to unravel information of the ancient magnetic field.

► Geomagnetic Field

Paleocortex

Definition

The paleocortex (Greek for old cortex) is a phylogenetically older type of cortex with less than the six layers seen in the neocortex, but more than the three layers seen in the archicortex (hippocampal formation). The parahippocampal gyrus has cortex of this type.

Paleoencephalon

Definition

The paleoencephalon describes phylogenetically older parts of the cerebral hemisphere that evolved along with the olfactory system. Sometimes the term rhinencephalon is used as a synonym. In the strict olfactory sense, the paleoencephalon would include the olfactory bulb, anterior olfactory nucleus, olfactory tubercle, and portions of the amygdala and nearby piriform cortex.

Paleoneurology

Definition

The study of the endocasts of fossil animals.

- Evolution of the Brain in Humans – Paleoneurology

Paleopallium

Definition

The palopallium refers to the cortex of the paleoencephalon, i.e., paleocortex (see above).

Paleopallium and Archipallium

- Evolution of the Pallium: in Amphibians

Pallia Dorsale and Piriforme

- Evolution of the Pallium: in Amphibians

Pallial Amygdala

Definition

Portion of the amygdaloid complex derived from pallial regions. It possesses layered cortical and nuclear components in amniotes, whereas only a nuclear portion is present in anamniotes (anurans amphibians).

- Evolution of the Amygdala: Tetrapods

Pallial Primordia

- Evolution of the Pallium: in Amphibians

Palliative

- Placebo Analgesic Response

Pallidum

- Globus pallidus
- Diencephalon

Pallidum, Ventral

Definition

A rostroventral extension of the globus pallidus that protrudes into the basal forebrain and olfactory tubercle beneath the anterior commissure. The ventral pallidum receives projections from the accumbens and medium cell (striatal) districts of the olfactory tubercle and projects to the lateral hypothalamus, medial extremity of the subthalamic nucleus, ventral tegmental area and adjacent medial part of the substantia nigra and ventrolateral part of the periaqueductal gray.

- Hypothalamus
- Hypothalamus, Lateral
- Striatopallidum

Pallium

Definition

The roof of the forebrain (telencephalon) which includes the cerebral cortex, hippocampus, olfactory cortex, claustrum, and some amygdalar groups – pallial is the adjective.

- Evolution of the Brain in Reptiles
- Evolution of the Wulst

Pallium (Medial, Dorsal)

Definition

The dorsal portion of the telencephalon with a cytoarchitectural organization that is primarily cortical (suggestively layered).

► Evolution of Hippocampal Formation

This creates a neuronal feedback circuit, which is called the Papez neuronal circuit and plays a role in memory formation. Being a vital component of the Papez neuronal circuit, the hippocampus is involved in memory formation. Lesions result in loss of the ability transfer the contents from short-term memory to long-term memory (anterograde amnesia).

► General CNS

Palmitoylation

Definition

Addition of palmitic acid, a saturated fatty acid containing 16 carbon molecules via an enzymatic reaction involving a Palmitoyl-acyl transferase enzyme.

Palmitic acid is covalently attached to proteins via thioester bonds at cytosolic cysteine residues and it is reversible reaction.

► Receptor Trafficking

Par Protein

Definition

Partitioning defective (Par) proteins include par-3, par-6, cdc42, and atypical protein kinase-C (aPKC). These proteins form a complex that exhibits a polarized distribution in the cell and is involved in establishing cellular polarity.

PAN/PVC Tube

Definition

Semipermeable polyacrylonitrile/polyvinylchloride polymer guidance tube for placing cells within and transplantation to the spinal cord.

► Transplantation of Olfactory Ensheathing Cells

Parabolic Flight

Definition

A flight trajectory of parabolic climbs and dives in which the aircraft and its contents are in free fall during the pushover periods, simulating a 0 g environment in the sense that objects in the aircraft are weightless. The length of the weightless phases depends on the air speed of the aircraft.

► Autonomic Function in Space
► Proprioception Effect of Gravity

Parabrachial Area

Synonyms

► Nuclei parabrachiales; ► Parabrachial nuclei

Definition

The parabrachial area comprises three nuclear areas:

- Lateral parabrachial nucleus
- Medial parabrachial nucleus
- Kolliker-Fuse nucleus

Papez Neuronal Circuit

Definition

The mammillothalamic fasciculus, Vicq d'Azyr bundle conducts efferents of the mammillary body to the thalamus (anterior thalamic nucleus). This in turn projects via the cingulum to the hippocampus, while the latter projects back via the fornix to the mammillary body and anterior thalamic nucleus.

Brainstem second relay station both for taste and visceral sensory pathways located in the pons. It is formed by several nuclei. The medial parabrachial area receives gustatory afferents from the nucleus of the tractus solitarius while the lateral parabrachial receives visceral afferents both vagal and from the area postrema. It is considered a primary site for taste– visceral integration relevant for conditioned taste aversion acquisition in rodents.

- ▶ [Conditioned Taste Aversion](#)
- ▶ [Diencephalon](#)
- ▶ [Parabrachial Nuclei](#)

Parabrachial Complex

Definition

A compact cluster of relay nuclei located rostrally in the dorsolateral pons, surrounding the middle cerebral peduncle (brachium conjunctivum). Individual nuclei within the parabrachial complex receive various ascending axonal inputs that provide information about viscerosensory function, metabolic status, and pain (arriving from nuclei in the spinal cord, nucleus of the solitary tract, and other brainstem sites). This ascending information is integrated with substantial descending inputs from the hypothalamus, amygdala, bed nucleus of the stria terminalis, and other brain sites. Different nuclei within the parabrachial complex deliver this integrated information to subcortical regions of the forebrain (primarily to subnuclei within the amygdala, hypothalamus, thalamus, and basal forebrain), and to nuclei in the midbrain and brainstem, thus influencing processes that include ingestive behavior, arousal, emotion, and autonomic function.

Parabrachial Nuclei

Definition

Latin: Nuclei Parabrachiales; Nuclear complex that is located in the dorsolateral tegmentum of the pons and serves as a major relay center for converging visceral, nociceptive, and thermoreceptive information to the forebrain. The parabrachial complex includes several subnuclei involved in taste sensation and control of

gastrointestinal, cardiovascular activity, and respiratory functions.

- ▶ [Central Regulation of Autonomic Function](#)
- ▶ [Parabrachial Area](#)

Paradoxical Embolism

Definition

Cardiac embolism that contains material from the venous system and reached the arterial system through a cardiac shunt.

- ▶ [Ischemic Stroke](#)
- ▶ [Stroke](#)

Parahippocampal Gyrus

Synonyms

- ▶ [Gyrus parahippocampalis](#)

Definition

The gyrus marks the transition from hippocampus with its allocortex to the isocortical structure of the temporal lobe. A cross-section shows four discrete cortical regions: presubiculum and parasubiculum on the hippocampal sulcus, entorhinal area and the perirhinal cortex deep in the calcarine sulcus.

- ▶ [Telencephalon](#)

Parallel Arrangement

Definition

A combination of two rheological elements, such that the elongation is common to both and the forces are to be added to obtain the force of the combined element.

- ▶ [Mechanics](#)

Parallel Processing

Definition

In the brain information is processed not only in one stream as in a typical computer but in many parallel and independent streams. Good examples are the different sensory pathways.

- ▶ Motor Unit
- ▶ Spasticity
- ▶ Tendon Reflex

Parallel Visual Processing Streams

- ▶ Visual Processing Streams in Primates

Parallelism

Definition

Mental and physical events run parallel to each other without any causal relations obtaining between mental and physical events.

- ▶ Causality

Paralysis

Definition

Severe loss of motor strength resulting from damage to ▶ **motor units** or to descending tracts impinging on them. Lower motoneuron paralysis presents with possible involvement of individual muscles, severe atrophy, flaccidity and ▶ **hypotonia** with absent ▶ **tendon reflexes**, possible ▶ **fasciculations** and ▶ **fibrillations**. Upper motoneuron paralysis usually presents with diffuse distribution of affected muscles, little atrophy, ▶ **spasticity**, ▶ **Babinski sign**, ▶ **fasciculations**.

- ▶ Babinski Reflex
- ▶ Fasciculations
- ▶ Fibrillations
- ▶ Motoneuron

Paralysis Agitans

Definition

- ▶ Parkinson Disease

Paralytic Ileus

- ▶ Bowel Disorders

Paramedian Pontine Reticular Formation (PPRF)

Definition

Anatomically, the PPRF is just the medial portion of the pontine reticular formation (<2 mm from the midline in macaques), but in the oculomotor literature, the PPRF is a functional unit that contains many of the neuronal populations and much of the neuronal circuitry involved in the generation of (mainly horizontal) eye movements. It first came to prominence when it was shown that lesions of the PPRF eliminated or drastically impaired most horizontal eye movements. The PPRF includes most elements of the brainstem burst generator involved in the generation of horizontal saccades, namely excitatory burst neurons, long-lead burst neurons, omnipause neurons, and arguably, inhibitory burst neurons which are on the pontomedullary border.

Intermixed with these neurons are saccade-related neurons that project to the cerebellum, and reticulospinal neurons that mediate head movements and eye-head coordination. Embedded in the PPRF are other nuclei that are usually considered to be distinct from the reticular formation. The most important is the abducens nucleus, which contains lateral rectus motoneurons and internuclear neurons that project to

medial rectus motoneurons. There are also circumscribed precerebellar relay nuclei that convey oculomotor signals to the oculomotor vermis, fastigial nucleus, and the floccular lobe, namely raphe pontis, the intrafascicular nucleus, the rostral pole of the abducens nucleus, and medial nucleus reticularis tegmenti pontis. Finally, the PPRF contains the fibers connecting these and other oculomotor structures (e.g., the superior colliculus and the vestibular nuclei), so the drastic effects of lesions are a product of destroying both the neuronal populations and the inputs to these populations.

- ▶ Brainstem Burst Generator
- ▶ Cerebellum – Role in Eye Movements
- ▶ Long-Lead Burst Neurons (LLBNs)
- ▶ Omnipause Neurons
- ▶ Saccade, Saccadic Eye Movement
- ▶ Superior Colliculus
- ▶ Vestibular Nuclei

Parameters

Definition

Constants or variables that are not conditioned by natural laws but define essential characteristics of the system's behavior under the action of the laws.

- ▶ Equilibrium Point Control

Parametric Control

Definition

- ▶ Equilibrium Point Control

Paramyotonia Congenita

Definition

- ▶ Non-dystrophic myotonias

Paraphasia

Definition

Incorrect use of words occurring in conduction aphasia.

- ▶ Aphasias

Paraplegia

Definition

Bilateral paralysis of the lower body including the two legs, most commonly resulting from damage to the spinal cord (complete transection), spinal nerve roots or peripheral nerves.

Parasomnias

Definition

Undesired physical events that occur during the entry into sleep, within sleep or during arousals from sleep. They include sleep walking and sleep terrors.

- ▶ Sleep-Wake Cycle

Parasthesia

Definition

Altered sensation, usually ascribed to pins and needles or tingling but which can also be ascribed to burning or pricking.

- ▶ Proprioception: Effect of Neurological Disease

Parasympathetic

- ▶ Central Integration of Cardiovascular and Respiratory Activity Studied In Situ

Parasympathetic Ganglia

► Autonomic Ganglia

Parasympathetic Nervous System

Definition

Parasympathetic refers to the branch of the autonomic nervous system that arises from specific cranial nerve nuclei and from the sacral spinal segments. This system supplies visceral organs with specific functions, such as the sphincter pupillae and the ciliary body in the eye, secretory glands producing fluid including acid in the stomach, enhancing motility of stomach and distal colon, bladder, etc.

► Ageing of Autonomic/Enteric Function

► Autonomic Ganglia

► Autonomic Reflexes

► Parasympathetic Pathways

The facial nerve branch project to the pterygopalatine and the submandibular ganglia (their neurons innervate the lachrymal, the submandibular and the sublingual glands), and the glosso-pharyngeal branch project to the otic ganglion (its neurons innervate the parotid gland). The fibers from the nucleus ambiguus and dorsal vagal nucleus enter the vagus nerve, of which they represent the motor component, and extend a long distance in the neck, thorax and upper part of the abdomen. The fibers terminate synapsing on neurons in small ganglia close to the tracheal and bronchial muscles and the esophagus and in some enteric ganglia of stomach and intestine. From these minute intramural ganglia, post-ganglionic fibers emerge that innervate glands and smooth musculature of airways, esophagus and gastro-intestinal tract. In the spinal cord, preganglionic parasympathetic neurons are assembled into columns in the second, third and fourth sacral segments. Their preganglionic fibers, predominantly cholinergic, project onto pelvic ganglia, whose post-ganglionic fibers innervate mainly the urogenital organs. In some organs, typically the heart or the pupil, which receive both sympathetic and parasympathetic fibers, these exert antagonistic effect. Many organs, however, are controlled predominantly by one or the other of the two pathways.

► Sympathetic Pathways

Parasympathetic Pathways

Definition

Beside the sympathetic pathways, the parasympathetic pathways are the second major component of the autonomic nervous system (there are also enteric pathways and an afferent or sensory component). Some parasympathetic pathways involve brain stem and cranial ganglia, and some are centered on the sacral region of the spinal cord and the pelvic ganglia.

In the brain stem the main nuclei of the parasympathetic pathways (the cranial parasympathetic outflow) are the Edinger-Westphal nucleus, the superior and inferior salivatory nuclei, dorsal vagal nucleus and nucleus ambiguus. The neurons of these nuclei issue axons then enter the oculomotor nerve, the facial, the glosso-pharyngeal nerve and vagus nerve, respectively.

The oculomotor branch projects to the ciliary ganglion (its neurons innervate the iris and the ciliary muscle, hence providing accommodation and pupil constriction).

Paraventricular Nucleus (PVN)

Definition

A subdivision of the hypothalamus located adjacent to the third ventricle. The PVN contains many distinct neurosecretory cells that regulate important physiological functions in the neuroendocrine system. These cells can be anatomically and functionally divided into a magnocellular division and a parvocellular division.

Magnocellular neurons produce the hormones oxytocin and vasopressin and project to the posterior pituitary gland. Parvocellular neurons that synthesize corticotrophin releasing hormone project to the median eminence at the ventral surface of the brain where they release peptides into the blood vessels of the hypothalamo-pituitary portal system, vasculature that carries peptides to the anterior pituitary gland. Some neurons, projecting to autonomic nuclei of the brainstem and spinal cord, are activated, in a stimulus-specific fashion, by hypoglycemia, hypovolemia, cytokines, pain, and environmental stressors. The PVN receives

afferent projections from multiple brain areas, such as the brainstem and other hypothalamic regions, that provide information about the homeostatic state of the organism.

- ▶ Central Regulation of Autonomic Function
- ▶ Hypothalamo-neurohypophysial System
- ▶ Hypothalamo-pituitary-adrenal Axis, Stress and Depression
- ▶ Hypothalamus
- ▶ Pituitary Gland
- ▶ Ventrolateral Preoptic Nucleus (VLPO)

Paravertebral Ganglia

Definition

The paravertebral ganglia are interconnected autonomic ganglia that lie close to the spinal nerves and the vertebrae, from the lower cervical/upper thoracic level to the sacral level of the spinal cord. The chains of paravertebral ganglia are paired, and lie just lateral to the bodies of the vertebrae.

- ▶ Autonomic Ganglia
- ▶ Sympathetic Nervous System
- ▶ Sympathetic Pathways

Paresis

Definition

A weakening of a muscle due to pathology of the muscle, the motoneurons that innervate it, or the efferent nerve that carries the latter's axons.

Paresthesia

Definition

Abnormal sensory experiences such as numbness, pins-and-needles sensations and tingling, occurring

spontaneously without external sensory stimulation and with some sensory ▶ [peripheral neuropathies](#).

- ▶ [Peripheral Neuropathies](#)

Parietal Lobe

Synonyms

- ▶ Lobus parietalis

Definition

Extends from the central sulcus to the parietooccipital sulcus.

- ▶ Telencephalon

Parietal Organ

Definition

A heritage of ancient, sea bottom-dweller vertebrates, an “eye” on the top of the head, the pineal body evolved in correlation with it.

- ▶ [Evolution of the Brain: At the Reptile-Bird Transition](#)

Parinaud Syndrome

Definition

This syndrome results from dorsal midbrain lesions and is characterized by impaired vertical eye movements (especially upwards) and absence of the pupillary light reflex.

- ▶ [Pupillary Light Reflexes](#)

Parkinson Disease

ALI SAMII

Department of Neurology, University of Washington Medical Center, Seattle, WA, USA

Synonyms

Idiopathic Parkinson's disease; Idiopathic Parkinsonism

Definition

A progressive neurological disease named after James Parkinson.

Characteristics

Clinical Features, Epidemiology, and Etiology

The four cardinal features of Parkinson disease are tremor, bradykinesia, rigidity, and ►postural instability. ►Parkinsonism is a non-specific term used to describe a constellation of signs on physical examination similar to those seen in Parkinson disease. Parkinson disease is defined as asymmetric Parkinsonism with no known cause, characterized by most of the four cardinal features, and responsive to anti-Parkinson medications (usually ►dopaminergic drugs) [1]. The diagnostic criteria for Parkinson disease have become more rigorous with gradations of diagnostic certainty. Any one of resting tremor, rigidity, or bradykinesia would suggest clinically possible Parkinson disease. Any two of the four cardinal signs (especially if asymmetric) would suggest clinically probable Parkinson disease. Clinically probable Parkinson disease with significant improvement in motor signs with dopaminergic drugs would suggest clinically definite Parkinson disease. The non-motor features of Parkinson disease include loss of sense of smell, depression, anxiety, autonomic dysfunction (constipation, urinary urgency, sexual dysfunction, orthostatic hypotension), sleep disturbance, including ►rapid-eye-movement (REM) sleep behavior disorder, and cognitive impairment. The non-motor symptoms of Parkinson disease are gaining much more attention than before since they contribute greatly to disability as the disease progresses and they do not respond to dopaminergic drugs.

The prevalence of Parkinson disease in industrialized countries is estimated at 0.3% of the general population and approximately 1% of the population aged over 60 [2]. The prevalence is slightly higher in men than in women. The mean age of onset is about 60, but approximately 5% of patients have young onset Parkinson disease, with motor symptoms appearing before age 40. *The pathology underlying the motor symptoms of PD is injury to the dopaminergic projections from the*

substantia nigra pars compacta to the striatum. Lewy Bodies are the pathological hallmarks of PD, but they are not confined to the substantia nigra. Pathology is widespread in PD and involves the amygdala, the olfactory bulb, dorsal motor nucleus of the vagus nerve, locus ceruleus, pedunculopontine nucleus, raphe nuclei, the cortex, and the peripheral autonomic nervous system. This extensive pathology may account for the non motor symptoms of PD. The etiology of PD is unknown, but aging, environmental factors, and genetic predisposition probably all play a role in causing Parkinson disease [3]. The recent discovery of several genetic loci related to familial Parkinson disease has led to the hypothesis that failure of the ►ubiquitin-proteasome system and protein misfolding are the final common pathways in the pathogenesis of Parkinson disease [4]. Mutations of the leucine-rich repeat kinase 2 (LRRK2) gene are the most common identifiable cause of Parkinson disease, in that 1% of patients without a family history and more than 5% of patients with a first degree relative with Parkinson disease have a LRRK2 mutation [5].

Medical Treatment of Motor Symptoms

There is no definitive agent known to slow down disease progression at the cellular level in Parkinson disease [6]. Therefore, treatment remains symptomatic with mostly dopaminergic drugs. A pilot study suggested that high dose ►coenzyme Q10 may slow symptom progression in early Parkinson disease [7]. These results have yet to be confirmed in larger studies with longer follow-up periods. Treatment is typically initiated when motor symptoms cause disability. The treatment of early Parkinson disease is with either a monoamine oxidase-B (MAO-B) inhibitor (selegiline or rasagiline), a non-ergot-derived dopamine agonist (pramipexole, ropinirole, transdermally absorbed rotigotine) or levodopa [8]. MAO-B inhibitors are generally safe and well tolerated, although there are warnings about certain drug interactions and tyramine containing foods when using MAO-B inhibitors. Side effects of dopamine agonists include nausea, hypotension, leg edema, vivid dreams, hallucinations (especially in the older population with cognitive deficits), somnolence (even sleep attacks), and disinhibited behavior (such as gambling). Dopamine agonists have more antiparkinson efficacy than MAO-B inhibitors, but they are less effective than levodopa. Treatment with an MAO-B inhibitor combined with a dopamine agonist may control motor symptoms for the first 2–5 years, but the likelihood of requiring levodopa after that increases significantly.

Levodopa remains the most potent anti-parkinson drug and is the backbone of therapy throughout much of the course of the disease. It is the preferred initial drug

in the older population and those with cognitive deficits or serious co-morbid conditions. Levodopa is combined with carbidopa or benserazide to prevent peripheral conversion to dopamine by dopa-decarboxylase. Side effects of levodopa are similar to those of dopamine agonists, except that somnolence, hallucinations, and leg edema are less common. Complications of long-term levodopa therapy include ▶**motor fluctuations**, including “▶**end-of-dose wearing off**”, and dyskinesia [9]. Dividing protein intake throughout the day may help reduce motor fluctuations. Controlled-release forms of levodopa may provide a longer duration of benefit, but their absorption is more unpredictable than immediate-release levodopa. ▶**Catechol-O-methyl transferase (COMT)** inhibitors, entacapone or tolcapone, prolong the half-life of circulating levodopa and improve end-of dose wearing off. Dyskinesia can be reduced by decreasing levodopa dosage, but at the expense of worsening motor symptoms. In a patient with motor fluctuations and dyskinesia, adding a dopamine agonist to levodopa may help reduce motor fluctuations. It may also allow for levodopa reduction, which in turn alleviates dyskinesia. The subcutaneously injectable dopamine agonist, apomorphine, is useful for rapid treatment of “off” periods in Parkinson disease. However, given the severity of apomorphine-induced nausea, premedication with domperidone or trimethobenzamide is needed. Amantadine may help suppress dyskinesia. MAO-B inhibitors may also be added to levodopa to help alleviate motor fluctuations.

Medical Treatment of Non-Motor Symptoms

Non-motor symptoms in Parkinson disease may occur as part of the disease or as complications of treatment [10]. These include depression, cognitive impairment, psychosis, constipation, sleep disturbance, orthostatic hypotension, drooling, and urinary symptoms. Depression in Parkinson disease is usually treated with a selective serotonin reuptake inhibitor (SSRI). There are no controlled head-to-head studies to suggest one SSRI is superior to another in Parkinson disease. Constipation should be treated aggressively using multiple modalities such as stool softeners, increased fiber intake, and suppositories. Disorders of sleep in Parkinson disease include daytime somnolence, sleep attacks, night-time awakenings due to over night bradykinesia, rapid eye movement (REM) behavior disorder, and restless legs/periodic limb movements. Daytime somnolence and sleep attacks may be associated with dopamine agonists and the agonist may have to be stopped. Overnight bradykinesia and restless legs may be alleviated with a bedtime dose of long acting levodopa sometimes with entacapone, or a dopamine agonist. Clonazepam is effective in treating REM behavior disorder. Psychosis in Parkinson disease is thought to be mostly drug-induced, and it occurs more frequently in demented patients.

Dopamine agonists are more likely to cause hallucinations than levodopa. First, the agonist and/or anticholinergic agent should be stopped, and the lowest dose of levodopa should be used. Adding an ▶**atypical neuroleptic** may be necessary. Quetiapine is the more popular atypical neuroleptic in Parkinson disease. It has fewer extrapyramidal adverse effects than risperidone and olanzapine and there is no need for weekly or bi-weekly blood count measurements that would be required with clozapine. ▶**Centrally acting cholinesterase inhibitors** (rivastigmine, donepezil, and galantamine) are somewhat effective in treating the dementia associated with Parkinson disease. Rivastigmine is more commonly used because the data to support its efficacy in Parkinson disease are more robust. Treatment options for hypotension include reducing the dosage of antiparkinson medications, increased salt and fluid intake, and adding fludrocortisone or midodrine. Drooling may be reduced by the peripheral anticholinergic agent, glycopyrrolate, but this drug may worsen constipation. Injection of botulinum toxin into salivary glands improves drooling. Urinary urgency may be treated with peripheral anticholinergic agents (oxybutynin and tolterodine) or alpha-adrenergic blocking agents (prazosin and terazosin). Unfortunately, the former worsen constipation and the latter exacerbate hypotension.

Surgical Treatment of Motor Symptoms

Deep brain stimulation of “hyperactive” nuclei relieve motor symptoms in patients who have severe motor fluctuations and dyskinesia [9]. High frequency stimulation of deep brain targets presumably reduces neural activity in tissue surrounding the electrode contact. The “suppression” of the target induced by deep brain stimulation can be sculpted by adjustments of the electrode configuration, stimulation intensity, pulse width, and frequency. Bilateral stimulation of the globus pallidus internus (GPi) or the subthalamic nucleus (STN) is effective in relieving motor symptoms. Some claim that bilateral STN stimulation is superior to bilateral GPi stimulation because it allows a reduction in antiparkinson medications, but there is continued debate about the optimal stimulation target for Parkinson disease. A large randomized multi-center study comparing bilateral STN to bilateral GPi stimulation in 300 patients with Parkinson disease is currently under way in the United States, the results of which should be available by 2009. Adverse effects of deep brain stimulation surgery include brain hemorrhage, infarct, seizures, and death. Other complications include lead breakage, other hardware failure, pulse generator malfunction, and hardware infection. Side effects from the stimulation itself include worsening dyskinesia, paresthesias, and cognitive, mood, speech, and gait disturbances. The stimulation-related side effects may be reversible by adjusting stimulation

parameters. The key to successful outcome is appropriate patient selection. The surgical patient must have clinically definite Parkinson disease with documented motor improvement on levodopa. There should be no dementia, untreated psychiatric condition, or serious medical illness. ► **Fetal mesencephalic** tissue transplantation has been studied in Parkinson disease. Although there was marginal improvement in some patients, disabling dyskinesia occurred in many patients. Therefore, fetal mesencephalic tissue transplantation is not a treatment option for Parkinson disease at present.

References

- Samii A, Nutt JG, Ransom BR (2004) Parkinson's disease. *Lancet* 363(9423):1783–1793
- de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C, Hofman A (2000) Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 54 (11 Suppl 5):S21–S23
- Litvan I, Chesselet MF, Gasser T, Di Monte DA, Parker D Jr, Hagg T, Hardy J, Jenner P, Myers RH, Price D, Hallett M, Langston WJ, Lang AE, Halliday G, Rocca W, Duyckaerts C, Dickson DW, Ben-Shlomo Y, Goetz CG, Melamed E (2007) The etiopathogenesis of Parkinson disease and suggestions for future research. Part II. *J Neuropathol Exp Neurol* 66(5):329–336
- Olanow CW, McNaught KS (2006) Ubiquitin-proteasome system and Parkinson's disease. *Mov Disord* 21(11):1806–1823
- Schapira AH (2006) The importance of LRRK2 mutations in Parkinson disease. *Arch Neurol* 63(9):1225–1228
- Biglan KM, Ravina B (2007) Neuroprotection in Parkinson's disease: an elusive goal. *Semin Neurol* 27(2):106–112
- Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos JL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M (2002) Parkinson study group. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 59(10):1541–1550
- Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C (2006) European federation of neurological societies; movement disorder society-European section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section. Part I: early (uncomplicated) Parkinson's disease. *Eur J Neurol* 13(11):1170–1185
- Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C (2006) European federation of neurological societies; movement disorder society-European section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson's disease. *Eur J Neurol* 13(11):1186–1202
- Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, Shulman LM, Gronseth G, Weiner WJ (2006) Quality standards subcommittee of the American academy of neurology. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the quality standards subcommittee of the American academy of neurology. *Neurology* 66(7):996–1002

Parkinsonism

Definition

Syndrome characterized by rigidity, tremor, and bradykinesia, of which Parkinson disease is the most common cause.

► Parkinson Disease

Parosmia

Definition

Distorted perception of smells in the presence of an odor source. Many patients not only suffer from quantitative olfactory dysfunction (anosmia, hyposmia), but also experience qualitative olfactory dysfunctions, classified under terms such as dysosmia or olfactory distortion.

These distortions can be roughly divided into parosmias (also called troposmia) and phantosmias with the major difference that distorted olfactory sensations are experienced in the presence (parosmia) or absence of an odor (phantosmia), respectively. Patients suffering from parosmia have distorted sensations of smell elicited by an odorant, therefore it is also called stimulated olfactory distortion. Parosmia is described as a qualitatively “wrong” perception of odors. For example, a patient may perceive the smell of rotten eggs whenever he takes a smell at roses. In most cases, the “wrong” smell is considered unpleasant. Parosmia is typically, but not always associated with quantitative olfactory loss (hyposmia). Parosmia mainly occurs in combination with post-traumatic or post-infectious olfactory loss. Rare causes of parosmia such

as brain tumors, side-effects of drugs, paraneoplastic syndromes, endocrine disorders, neurologic disorders, psychiatric disorders or intracerebral haemorrhage have been reported. Although the exact site of the generation of parosmia remains unknown, most parosmias are likely to be generated at the level of the olfactory epithelium and/or the olfactory bulb. On the other hand, parosmia may also be a problem of the central nervous system. Important clinically is the observation that most parosmic impressions tend to diminish over months and finally disappear after years.

- ▶ Olfactory Pathways
- ▶ Smell Disorders

Paroxysmal Extreme Pain Disorder (PEPD)

Definition

Previously referred to as familial rectal pain. The severe pain in PEPD patients along with redness in the lower body can start in infancy (and possibly in utero), and is induced by defecation or probing of the perianal areas, and is accompanied sometimes by tonic non-epileptic seizures, syncopes, bradycardia and occasionally asystole.

Pain progresses with age to ocular and maxillary/mandibular areas and is triggered by cold, eating or emotional state. Pain episodes can last seconds to minutes (and hours in extreme cases), and gradually subside over minutes.

- ▶ Voltage-gated Sodium Channels: Multiple Roles in the Pathophysiology of Pain

Paroxysmal Hemicrania (PH)

Definition

Rare headache belonging to the group of ▶ [trigeminal autonomic cephalalgias](#) and is characterized by severe, unilateral pain attacks localized to orbital, supraorbital, and temporal areas, lasting 2 to 30 minutes, and accompanied by ipsilateral ▶ [autonomic](#) features.

- ▶ Headache

Pars Tubualis

Definition

An area of the pituitary stalk rich in melatonin receptors.

- ▶ Melatonin

Partial Seizures (Focal Seizures)

Definition

These seizures are characterized by focal motor or sensory symptoms indicating the location of brain lesions. For instance, aversive seizures characterized by deviation of eyes or head to one side indicate a focus in the opposite ▶ [prefrontal cortex](#). Focal (Jacksonian) motor seizures may result from localized lesions (injury or tumor) to the contralateral ▶ [primary motor cortex](#) (M1) and may start as local rapid (clonic) contractions, often at a finger, great toe or mouth corner, and then spreading over the body with loss of consciousness (Jacksonian march).

- ▶ Jacksonian Motor Seizures
- ▶ Prefrontal cortex
- ▶ Primary Motor Cortex (M1)

Parvocellular Cells

Definition

Small cells located in two to four layers of the LGN of primates that have been proposed to be part of a pathway (the P pathway) from the retina to visual cortex concerned with detail and color vision.

- ▶ Evolution of the Visual System: Mammals – Color Vision and the Function of Parallel Visual Pathways in Primates

Passband

Definition

The frequency region in which the magnitudes of sound are not attenuated by a filter.

- ▶ Acoustics

Passive Avoidance Learning

Definition

Passive avoidance is a task in which animals avoid an aversive stimulus by inhibiting a previously punished response (compare with Active avoidance learning).

Behaviors that are more compatible with natural defensive responses to aversive stimuli (see SSDR in glossary) are more easily learned.

► Active Avoidance Learning

► Aversive Learning

Patch Clamp

Definition

Erwin Neher and Bert Sakmann developed the patch clamp in the late 1970s and early 1980s. They received the Nobel Prize in Physiology or Medicine in 1991 for this work. This electrophysiological method allows to record ion channels' activity in an individual cell using a glass electrode with an open tip diameter of about 1 μm . There are three major configurations of this method. The "cell attached" mode (the glass pipette is tightly sealed on the cell membrane), the "excised configuration" (the patch of membrane isolated by the pipette is removed from the cell) and the "whole cell" configuration (the membrane under the pipette is broken, providing an access to the intracellular space of the cell). The "cell attached" and the "excised" configurations allow recording the activity of individual ion channels embedded in the patch of membrane isolated by the glass pipette. The "whole cell" configuration allows to record global electrical activity passing through the entire cell membrane. This technique can be used in the "voltage clamp" mode, keeping the voltage constant in order to see changes in the current. Conversely, it can be used in the "current clamp" mode, in order to see changes in the voltage.

► Intracellular Recording

Path Integration

Definition

A process of estimating one's own position in space by integrating (vectorially summing) the distances and

directions covered by previous self-movement (idiothetic inputs). This is also known as dead reckoning. The composite vector points from the start position to the current position. There are two forms of path integration: path integration with a map and path integration without a map. When path integration is used with a map it can be used to update the traveler's location on the map. Therefore, it is an important contributor to mapping. When path integration is used without a map it can only be used for returning to a start location, or "homing". This is done by the simple process computing the outbound vector from a start (home) location, inverting the composite vector and following the inverted vector. Homing by means of path integration has been shown in insects (ants) and rodents.

► Optic Flow

► Spatial Learning/Memory

Pathology

Definition

Pathology literally is the study of pathos (disease, suffering). Traditionally, pathology is a morphologic study of histological abnormalities detected by microscopic examination. More recently, pathology uses molecular, microbiological, and immunological techniques.

Pathology also means a condition produced by disease.

P

Pause Neurons (pns)

► Omnipause Neurons

Paw Preference

Definition

Preference of paw in taking food.

► Nervous, Immune and Hemopoietic Systems: Functional Asymmetry

Pax Genes

NORIKO OSUMI
Division of Developmental Neuroscience, CTAAR,
Tohoku University School of Medicine, Sendai, Japan

Definition

Pax genes are originally identified as homologs structurally related to the *Drosophila* pair-rule gene, *paired*, which encodes a ▶transcription factor [1]. There are nine members in the *Pax* gene family, which are categorized into four subclasses (Fig. 1) [2,3].

All members have a DNA-binding paired domain (PD) together with or without an octapeptide (OP), and the members except Pax1 and Pax9 have another DNA-binding homeodomain (HD). Group 1 (Pax1, Pax9) have only PD and OP, Group 2 (Pax2, Pax5, Pax8) have PD, OP, and incomplete HD, Group 3 (Pax3, Pax7) have PD, OP, and complete HD, and Group 4 (Pax4, Pax6) have PD and complete HD. PD consists of 6 alpha-helices, and is divided into two subdomains (N-terminal PAI domain and C-terminal RED domain), each recognizing distinct half-sites of the bipartite binding site in adjacent major grooves of the DNA helix [4].

Characteristics

Expression patterns of each *Pax* gene are highly region-specific, and observed in ▶CNS, ▶PNS, and various

ectodermal, mesodermal, and endodermal tissues. The importance of the *Pax* family in organogenesis can be assumed from various congenital diseases and cancers related to mutations of *Pax* genes and down- or up-regulation of *Pax* gene expressions [5]. Interestingly, there are spontaneous mouse mutants for *Pax1* (*undulated*), *Pax3* (*Splotch*), and *Pax6* (*Small eye*), which is quite in contrast with other transcriptional factors that are crucial in organogenesis. Since *Pax1* and *Pax9* are predominantly expressed in mesodermal tissues, and *Pax4* is more important in pancreatic development, the other members of the *Pax* family are taken into consideration here.

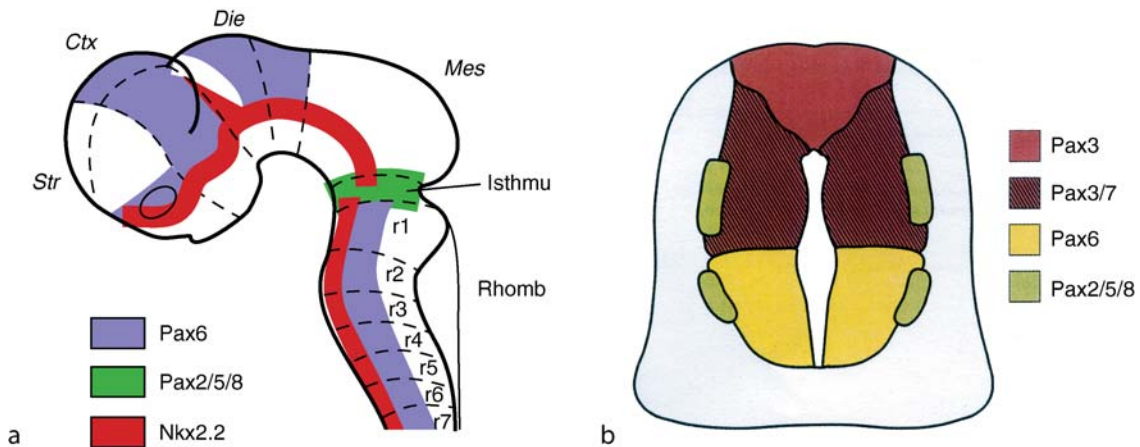
Pax2/5/8

Pax2, Pax5, and Pax8 are structurally close and work similarly. Pax5 is originally identified as BSAP (B-cell specific activator protein) that is essential for development of B-lymphocytes. Pax2/5/8 expressed in the boundary region between the midbrain and hindbrain (midbrain/hindbrain boundary: MHB; (Fig. 2a), and important in establishment of MHB that works as an organizer for brain patterning [6].

In ovo mis-expression of Pax2 and Pax5 by electroporation in chick embryos can change the fate of presumptive diencephalons to the tectum. Expression of Pax2, Pax5, En, Wnt1, and Fgf8 consists of a feedback loop at the MHB in formation of the optic tectum in the midbrain and of the cerebellum in the hindbrain. Similar machineries are also work in the formation of MHB in mammalian embryos, which is shown by the phenotype

Group	Pax genes	Basic structure			Localization		Mouse mutant		Human syndrome
		PD	OP	HD	Mouse	Human	Natural	Targeted	
Group 1	<i>Pax1</i>	N —  — C			2	20p11	<i>Undulated</i>		Spina bifida (?)
	<i>Pax9</i>				12	14q12-q13			
Group 2	<i>Pax2</i>	N —  — C			19	10q25	<i>1Neu Pax2</i>	Yes	Renal coloboma
	<i>Pax5</i>				2	2q12-q14			
	<i>Pax8</i>				4	9p13		Yes	
Group 3	<i>Pax3</i>	N —  — C			1	2q35	<i>Splotch</i>		Waaenburg syndrome I, III
	<i>Pax7</i>				4	1p36.2		Yes	
Group 4	<i>Pax4</i>	N —  — C			6	7q32		Yes	
	<i>Pax6</i>				2	11p13	<i>Small eye</i>	Yes	Aniridia Peters anomaly

Pax Genes. Figure 1 Structures and genomic positions of *Pax* genes. *Pax1-9* genes are categorized into four groups from their molecular structures. Natural mutations of *Pax* genes in the mouse and human diseases are also shown. PD paired domain; OP octapeptide; HD homeodomain.



Pax Genes. Figure 2 Expression patterns of *Pax* genes in the early neural tube. Schematic illustration of the lateral (a) and transverse (b) views showing region specific expression of *Pax* genes. (b) is taken from ref. [1]. Ctx cerebral cortex; Str striatum; Die diencephalon; Mes mesencephalon; r1-7 rhombomere 1-7.

of knockout mice of the genes. Pax2 and Pax5 are also expressed in the specific dorsoventral region of the developing neural tube (Fig. 2b) [7], and may be involved in specification of interneurons. Pax2 also works to establish the forebrain/midbrain boundary through interaction with Pax6 (see below). Mutation in *Pax2* is reported to be related to a kidney disease, renal coloboma.

Pax3/7

Pax3 and Pax7 are structurally close and work similarly. Pax3/7 is expressed in the dorsal region of the developing neural tube (Fig. 2b) [1] and the dermomyotome, an embryonic primordium of the muscle and dermis. Electroporated Pax3/7 forces the midbrain to differentiate into the tectum in chick embryos. Spontaneous mutant *Splotch* (*Sp*) mice have mutations in *Pax3* and show abnormalities in development of tissues originated from the neural crest that is formed at the most dorsal part of the neural tube. Heterozygous *Sp*^{+/+} mice show white spots in the abdomen, legs, and tail, which is due to abnormal development of melanocytes derived from the neural crest. Homozygous *Sp*/*Sp* mice show spina bifida (separated spinal bones), exencephaly (open brain), reduced or loss of dorsal root ganglia, and hypoplastic leg muscles [1-3]. Pax7 is expressed in neuronal cells of the optic tectum/superior colliculus. Neurons expressing Pax7 migrate towards the pia and concentrate in the stratum griseum superficiale, the target site for retinal axons.

In humans, patients of Waardenburg syndrome type 1 show mutation at 2q37, and those of type 3 show deletion in 2q35-37 covering *PAX3* gene [5]; both sets of patients suffer from hearing loss and abnormal skin color. The hearing loss of Waardenburg patients is thought to be caused by abnormal migration of neural crest cells into the otic primordium from the similar

phenotype seen in *Sp*^{+/+} mice. Involvement of *Pax3* and *Pax7* in cancer is also reported [5]. For example, alveolar rhabdomyosarcoma is caused by translocation of chromosomes including *PAX3* or *PAX7*.

Pax6

PAX6/Pax6 gene is first isolated as a responsible gene for human congenital aniridia (lack of the iris in the eye) and mouse *Small eye* mutant [8], and more intensively studied than any other *Pax* genes. *Pax6* gene is highly conserved throughout the phylogeny, and related to development of the sense organs, eyes, brain, pancreas, and pituitary gland [1-3]. In the early eye primordium, Pax6 is strongly expressed in the head ectoderm that will form the lens and cornea, and in the optic cup that will form the neural and pigment retina. Later in development, Pax6 is expressed in prospective ganglion-cells and amacrine-cells, but not in photoreceptors. Pax6 also influences eye development through a non-cell autonomous manner by regulating migration of neural crest cells.

In the vertebrate CNS, Pax6 is expressed in the forebrain, hindbrain, and spinal cord from the earliest stage of brain development. *Small eye* mice and rats are spontaneous *Pax6* mutant strains, homozygotes which lack the eyes and nasal structures. They also exhibit severe malformation in various brain regions where *Pax6* is expressed, showing the importance of the gene in brain patterning, neuronal migration, and axon extension [9,10]. For example, mutual repression of Pax6 and Pax2 defines the boundary between the forebrain and midbrain, and that of Pax6 and Gsh2 in the telencephalon establishes the boundary between the cerebral cortex and the striatum. In the dorsal telencephalon, Pax6 and *Emx1* show gradient expression patterns in opposite directions, thereby patterning the

telencephalon along the anterior-posterior axis. In the hindbrain and spinal cord, Pax6 is essential in specification of the ventral neurons: *Pax6* homozygous mutant mouse and rat embryos lack the hypoglossal nerve (a somatic motor nerve of the XIIth cranial nerves) and En1-expressing interneurons. Pax6 is involved in navigation of certain neurons such as mitral cells in the olfactory bulb and olfactory cortex neurons, which is done by non-cell autonomous manners. *Pax6* homozygous mutant rats show defects in thalamocortical projection, which may include Neurogranin signaling pathways.

In the adult brain, Pax6 is expressed in neurons of the olfactory bulb, amygdala, thalamus, and cerebellum [7]. Since homozygous *Pax6* mutants die at birth and therefore cannot survive into the postnatal stage, the function of Pax6 in the adult brain remains largely unsolved. It has recently been shown that Pax6 is important in postnatal neurogenesis by maintaining neural stem/progenitor cells; Pax6 heterozygous rats show decreased cell proliferation in the hippocampus and subventricular zone of the lateral ventricle. Pax6 can also promote neuronal differentiation, so it is likely that Pax6 works multifunctionally in highly context-dependent manners.

Known target/downstream molecules for Pax6 transcription factor in CNS are a bHLH transcription factor Neurogenin2, cell adhesion molecules L1 and R-cadherin, a secreted factor Wnt7b, a fucosyltransferase FucT9, and a fatty acid binding protein Fabp7 (BLBP). It is of interest that FucT is involved in the synthesis of LewisX carbohydrate epitopes that are used as markers in blastocysts, hematopoietic stem cells, and neural stem cells, and that Fabp7/BLBP is a well-known marker of radial glia and works to maintain embryonic stem cells. For patterning the brain, mutual repression of Pax6 and other transcription factors such as Pax2 (forebrain/midbrain regionalization), Gsh2 (cortex/striatum regionalization), and Nkx2.2 (somatic motor precursor domain formation) delineates distinct brain regions.

Clinically, expression of *PAX6* is reported to be significantly reduced in glioblastoma, the most common primary malignant brain tumors, molecular mechanisms of which remain unsolved.

References

1. Gruss P, Walther C (1992) Pax in development. *Cell* 69(5):719–722
2. Mansouri A, Stoykova A, Gross P (1994) *Pax* genes in development. *J Cell Sci Suppl* 18:35–42
3. Dahl E, Koseki H, Balling R (1997) *Pax* genes and organogenesis. *Bioessays* 19:755–765
4. Czerny T, Shaffner G, Busslinger M (1999) DNA sequence recognition by Pax proteins: bipartite structure of the paired domain and its binding site. *Genes Dev* 13(19):2048–2061

5. Chin N, Epstein JA (2002) Getting your Pax straight: Pax proteins in development and disease. *Trends Genet* 18(1):41–47
6. Nakamura H (2000) Regionalization of the optic tectum: combinations of gene expression that define the tectum. *Trends Neurosci* 24:32–39
7. Stoykova A, Gruss P (1994) Roles of *Pax*-genes in developing and adult brain as suggested by expression patterns. *J Neurosci* 14:1395–1412
8. Hanson I, Van Heyningen V (1995) Pax6: more than meets the eye. *Trends Genet* 11(7):268–272
9. Osumi N (2000) The role of Pax6 in brain patterning. *Tohoku J Exp Med* 193(3):163–174
10. Manuel M, Price DJ (2005) Role of Pax6 in forebrain regionalization. *Brain Res Bull* 66(4–6):387–393

PC Afferents

Definition

Rapidly adapting mechanoreceptive afferents (also called fast adapting type II) with large receptive fields, ending in relation to Pacinian corpuscles (PC).

- Pacinian Corpuscle
- Vibration Sense

PCD

- Programmed Cell Death

PDZ Domain

Definition

PDZ domain is a structural domain of 80–90 aminoacids found in signaling proteins, which provides structural integrity to protein signaling complexes and helps anchor transmembrane proteins to the actin cytoskeleton. There are approximately 200 PDZ containing proteins in the human genome.

PEA3

Definition

A member of the ETS class of DNA-binding transcription factors. EPEA3 is phosphorylated and activated by Ras via MAP kinase signaling pathways and regulates the expression of several genes in a variety of cell types.

► Neurotrophic Factors in Nerve Regeneration

Pediatric Pain

► Pain in Children

Pedophilic Perpetrators

Definition

Men who abuse children sexually for different reasons.

► Forensic Neuropsychiatry

Pedunculopontine Tegmental Nucleus

Synonyms

► Nucl tegmentalis pedunculopontinus (Ch.5)

Definition

An important nucleus from the cholinergic cell group of the lateral reticular formation. It has two parts:

- Pedunculopontine tegmental nucleus, compact part
- Pedunculopontine tegmental nucleus, diffus part

Pedunculopontine Tegmental Nucleus, Compact Part

Synonyms

► Nucl tegmentalis pedunculopontinus; Pars compacta

Definition

This densely packed part of the pedunculopontine tegmental nucleus lies in the caudo-lateral Mesencephalon and has reciprocal connections with the motor centers and the limbic system. Efferents go to the spinal cord. Electrical stimulation of this area causes coordinated locomotion ("mesencephalic locomotor region") in decerebrated animals.

► Mesencephalon

Pedunculopontine Tegmental Nucleus, Diffuse Part

Synonyms

► Nucl tegmentalis pedunculopontinus; Pars dissipata;
► Pedunculopontine tegmental nucleus; Dissipated part

Definition

In addition to the pedunculopontine tegmental nucleus, compact part, the pedunculopontine tegmental nucleus also contains a cholinergic region with loosely arranged cell bodies. But their function is not clear unlike that of the locomotor tasks of the compact part.

► Mesencephalon

Pelvic Afferents

► Visceral Afferents

Pelvic Floor

Definition

The pelvic organs are supported by striated muscles (levator ani and coccygeus) and connective tissue that close the caudal end of the abdomen spanning the space between the pubic bones anteriorly, the ischial spines laterally and the sacrum posteriorly.

► Micturition

Pelvic Nerve

Definition

The pelvic nerve connects the pelvic viscera (urinary bladder, urethra, distal bowel, vagina, uterine cervix) with the sacral S2-S4 (and in some species the lower lumbar) segments of the spinal cord. The nerve contains efferent autonomic neurons (mainly parasympathetic, but not entirely so), and also afferent nerves that convey sensory information to the central nervous system. It is responsible for the neural control of the hindgut, bladder and reproductive organs.

- ▶ Micturition
- ▶ Neurogenic Control
- ▶ Neurophysiology of Sexual Spinal Reflexes
- ▶ Visceral Afferents

Pendular Nystagmus

Definition

Nystagmus with a quasi-sinusoidal waveform (as opposed to “saw tooth” or “jerk” nystagmus in which there is alternation of slow and fast phases of nystagmus).

- ▶ Central Vestibular Disorders
- ▶ Nystagmus

Penetrance in Inheritance

Definition

In dominantly inherited disorders, penetrance refers to the proportion of persons with a mutation who show clinical symptoms. Complete penetrance refers to a situation where symptoms are present in everyone who has the mutation, and incomplete penetrance refers to a situation where symptoms are not always present in those with the mutation.

Penumbra

Definition

The marginally perfused area in the brain that surrounds the most deeply infarcted area during an ischemic stroke. This tissue is still viable if adequate perfusion can be maintained or restored.

- ▶ Ischemic Stroke
- ▶ Stroke

PEPD

Definition

- ▶ Paroxysmal Extreme Pain Disorder

Percept

Definition

The conscious experience of a sensory stimulus. The percept reflects stimulation of the sensory system (e.g. eye, ear, skin), but is also determined by higher-level cognitive processes (e.g. attention, memory).

- ▶ Perception

Perception in Vision

DIRK KERZEL

Faculté de Psychologie et des Sciences de l'Éducation,
Université de Genève, Genève, Switzerland

Definition

Perception is the conscious experience of sensory stimulation. The perceptual process begins with the transformation of the external stimulus energy into the firing of neurons. The sensory signals originating in the sense organs are analyzed into different perceptual attributes such as pitch, color, form, or motion.

What is perceived depends not only on the raw sensory signal, but also on higher-level cognitive processes such as attention and memory. These processes are not always conscious, and they organize and interpret the information coming from the eyes (vision), ears (audition), nose (olfaction), tongue (taste), skin (tactile sense), and inner ears (vestibular senses). As a result, we perceive meaningful objects and events that are defined in both space and time. The perceptual process is very different from a mere image taken by a camera because objects and events are recognized and thereby linked to previously acquired knowledge stored in memory.

Characteristics

Perception is our mind's window on the world. It enables us to create mental representations of objects (flowers, cars, etc.) or events (walks in a park, accidents, etc.), and enables us to interact with objects in the world. Vision is by far the most important sensory modality and this contribution is restricted to this modality. Nonetheless, most of the concepts presented here can be applied to other sensory modalities (audition, olfaction, taste, tactile and vestibular senses). The importance of vision is evident in the space allotted to it in the human neocortex: the primary visual cortex occupies about 15% of the neocortex, and more than 30 visual areas have been identified. Altogether, 60% of the human neocortex is involved in the processing of visual stimuli.

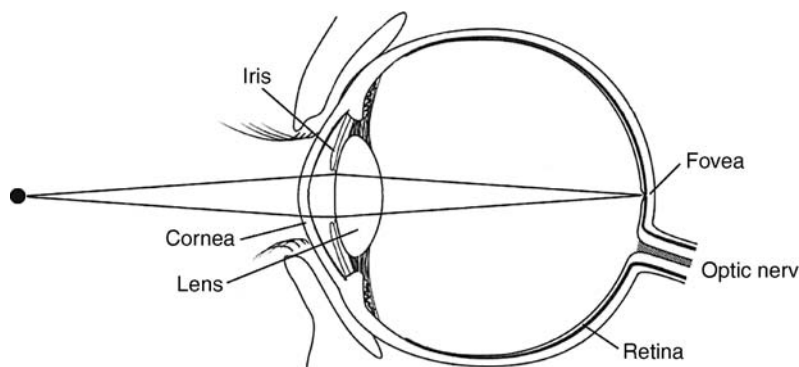
Intuitively, visual perception is a passive process; as soon as we open our eyes, we see the world around us. Another intuition about visual perception is that the basic units of visual perception are objects because we typically talk about objects (cars, flowers, etc.) when we report what we see. Both intuitions are wrong. Research in psychology and neurophysiology has shown that perception is a highly active process and that the attributes of an object such as its color or its movement are processed independently. The characteristic division of labor starts in the retina, and continues as visual

information is transmitted to the corpus geniculatum laterale (CGL) in the thalamus, and from there to the primary visual cortex. We will examine each of these stages in turn and show how complementary systems guarantee reliable perception under different conditions and for different purposes.

Light enters the eye through a small aperture, the pupil, and passes through the cornea and the lens before it reaches the retina (see Fig. 1).

Cornea and lens bring the image that is projected onto the retina into focus [1]. While the cornea has a larger focusing power (42 diopters), only the lens' focusing power (about 18 diopters) can be adjusted to bring objects into focus. To this end, the ciliary muscles contract and the curvature of the lens increases, a process that is called accommodation. A high curvature of the lens is associated with high focusing power that is necessary to project a clear image of nearby objects on the fovea. Across the lifetime, the lens loses elasticity and its maximal curvature decreases. As a consequence, a clear image would be projected on a plane behind the retina, but what is captured by the retina is blurred. This condition is known as presbyopia ("old eye"). Similar blurred retinal images result when the eye ball is too long or too short such that the focusing power of the lens is too weak or too strong, respectively. All these impairments may be corrected by glasses that either focus and thereby increase the focusing power of the optical system or disperse the light and thereby decrease its focusing power.

To be treated in the nervous system, the stimulus energy has to be transformed into electrical signals of neurons. In the visual modality, the process of transduction is achieved by two types of receptors: rods and cones. They are hidden behind a transparent layer containing amacrine, horizontal, bipolar and ganglion cells. The ganglion cells transmit the neuronal signals originating in the receptors to subcortical centers. Their axons leave the eye through an aperture in the retina



Perception in Vision. Figure 1 A cross section of the human eye. The light passes through a small aperture (pupil) and is focused by the cornea and lens. The rays of light reach receptors in the retina that are hidden behind a translucent layer of cells (not shown).

devoid of receptors, the blind spot. Although no visual information is received in this region, we do not perceive a “hole” in our visual field when we close one eye. The visual system fills the void rather actively by extrapolating visual information from the neighboring retina.

Light entering the receptor engenders a biochemical cascade when hitting a photopigment contained in the receptor. The electrical potential of the receptor changes as a result of the cascade. This process is extremely sensitive: A single photon may change the potential of the receptor and light is perceived when only seven receptors are stimulated simultaneously. However, receptors respond only to electromagnetic energy at wavelengths between 400 and 700 nm. Small wavelengths evoke the color blue, medium wavelengths the colors green and yellow, and long wavelengths the color red. Wavelengths shorter (e.g. X-rays) than 400 or longer than 700 nm (e.g. radio waves) are not absorbed by the receptors.

The two receptor classes, rods and cones, have very different characteristics and involve different neural circuits. Rods are larger than cones and contain a photopigment that responds best to light at a wavelength of 500 nm. That is, light of this wavelength evokes a response more easily than light with higher or lower wavelengths. In contrast, cones may contain one of three different photopigments that differ in their preferred frequency: the short wave pigment (419 nm), the medium-wavelength pigment (531 nm) and the long wavelength pigment (558 nm). Taken together, the three cone types respond best to a wavelength of 560 nm. The difference in the preferred wavelength of rods and cones is evident in the Purkinje phenomenon: The colors in the lower part of the spectrum seem brighter (e.g. green objects appear more salient) when seen under conditions where rods are active compared to conditions where cones are active.

Rods enable us to see at low light intensities, but do not contribute to our visual experience in the daylight. The rod's high sensibility is achieved by summing up signals across a large number of neighboring rods. While this strategy makes the system more sensitive, it produces a loss in spatial resolution. The activity of neighboring receptors cannot be discriminated and we only see blurred outlines in the dark. Also, the rod system cannot discriminate between different wavelengths and is therefore color-blind.

Cones are active during the daylight and do not contribute to nocturnal vision. They show far less summation across space than rods and thereby allow for the discrimination of spatial detail. Because the three types of cone receptors have different spectral sensitivities, they are differently activated by the incoming light. For instance, a monochrome yellow light of 575 nm will activate the long wavelength cone more than the medium and short-wavelength cones. The pattern of

activation of the three receptors is the basis for color vision and any physical stimulus that produces the same pattern of activity in the receptors will be perceived as equal (a so-called metamer color). For instance, a blend of medium and long wavelength is also perceived as yellow. If one of the cone types is missing due to a genetic deficiency, color vision is abnormal. Dichromats are predominantly male because the deficient gene is on the X-chromosome. They cannot discriminate between red and green and their color perception is limited to a continuum from blue to yellow or from blue to red, depending on the missing cone type.

The distribution of rods and cones across the retina is not uniform. While most of the retina contains both rods and cones, there is a small area located on the line of sight, referred to as fovea, which contains only cones. Few of the foveal cones (as few as one) converge on one ganglion cell and the density of cones and ganglion cells is higher than in the periphery. Therefore, the fovea is the retinal area with the highest spatial resolution (acuity). Most of what we consciously perceive is being projected on the fovea, in part because of the disproportionately large cortical representation of the fovea with respect to the rest of the retina. The cortical magnification of the fovea is due to the high density of ganglion cells in the fovea and to a larger cortical representation of ganglion cells projecting from the fovea.

The projections from the fovea to the cortex are highly ordered [2]. Adjacent locations on the retina will also be represented in adjacent locations in V1, a principle that is referred to as retinotopy. Cells in V1 combine the circular receptive fields of ganglion cells to form elongated receptive fields. The receptive field of a neuron refers to the area on the receptor surface from where the neuron receives information. While ganglion cells are maximally stimulated by small points of light, cells in V1 respond best to lines or bars. Cells in V1 have been classified according to their preferred stimulus. Simple cells in V1 respond best to bars of a certain orientation. Complex cells respond to oriented bars moving in a certain direction. End-stopped cells are selective to oriented bars of a certain length moving in a certain direction. Another characteristic of V1 is its organization into columns that share common processing characteristics. Location columns comprise neurons that respond to one particular location of the retina. Within such a location column, each eye is represented by two ocular dominance columns with neurons responding preferably to stimulation of the left or right eye. Finally, each ocular dominance column is composed of a complete set of orientation columns covering vertical to horizontal orientations. Neurons in an orientation column respond best to lines at a certain orientation.

While we do not directly perceive the representation of the stimulus in V1, V1 is necessary for conscious perception. Lesions of V1 lead to blindness in the

affected region. While this deficit, referred to as scotoma, eliminates conscious perception of stimuli presented in the respective visual area, it may not completely eliminate perceptual processing of those stimuli [3]. If patients who deny conscious perception of stimuli presented in the scotoma are forced to respond to these stimuli, their responses may show some residual sensitivity. For instance, they may be able to point to a stimulus presented in the scotoma with above chance (but far from perfect) performance. Even if cortical stimulus processing is precluded in this condition, retinal projections to a subcortical center in the midbrain are still intact. About 10% of the projections from the retina go to the superior colliculus, a structure that is also implied in the control of eye movements. Subcortical processing via this route may enable us to localize an object while circumventing consciousness.

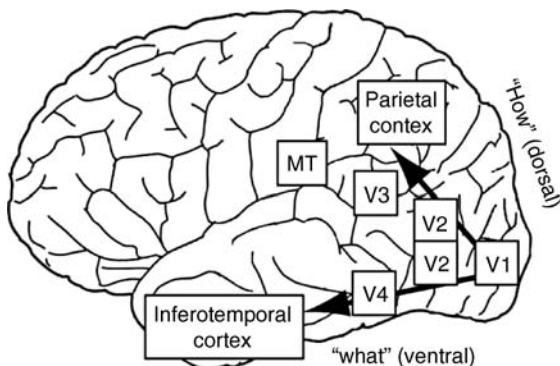
From V1, visual processing in the cortex continues along two major pathways: A ventral pathway from V1 to the inferotemporal cortex and a dorsal pathway from V1 to the posterior parietal cortex (see Fig. 2).

Even if there is considerable crosstalk between the two pathways, they show important functional specialization. The dorsal pathway is responsible for determining an object's location ("where" pathway), while the ventral pathway is responsible for determining an object's identity ("what" pathway). More recently, the dorsal pathway has been characterized as action pathway ("how" pathway) because it determines how a motor action is being carried out [4]. Obviously, information about where an object is located in space is crucial for successful motor interaction with it. A case study provided neuropsychological evidence for the distinction of "what" and "how." Patient DF suffered from damage to her ventral pathway after carbon monoxide poisoning. She was unable to identify simple geometrical forms or

to name objects, a condition known as visual form agnosia. For instance, she could not identify a screwdriver or describe the orientation of a slot. However, her actions toward these objects were unimpaired and she could place a card in the slot which cannot be done without information about its orientation. Presumably, information about the slot's orientation was available in the dorsal pathway that guided her actions, but not in the ventral pathway where conscious recognition of the object would usually take place. Conversely, patients with lesions in the posterior parietal area often show impairments in the visual guidance of actions, while object recognition is unimpaired.

The broad distinction between two visual pathways was further refined by the identification of cortical modules. Modules are cortical areas specialized in the processing of a particular perceptual dimension, such as form (see above), color, or motion in the visual modality. Damage to such a module results in an inability to perceive the respective dimension appropriately; a condition referred to as agnosia [5]. For instance, lesions of V4 make the perception of color difficult and patients perceive the world in shades of gray even if their cone system (see above) is intact. Lesions of V5 make the perception of motion impossible. In one such patient, moving objects appeared as static images in separate positions with no transitions between these positions. Thus, the patient was unable to pour a liquid into a glass because the liquid seemed to be frozen. Also, her interaction with other people was disturbed because she could not follow the movements of her interlocutor's mouth.

After demonstrating the modular, analytic processing of visual information, the intuitive unity of objects mentioned at the beginning requires further explanation. How can we perceive objects as basic units given that the brain analyzes objects into their component attributes? According to feature integration theory, the binding of attributes belonging to one and the same object requires attention [6]. That is, visual focal attention "glues" together the various properties of an object that are processed in a distributed manner in various modules. The role of attention has been studied using a paradigm referred to as visual search. In a typical trial, the observer is asked to look for a target, for instance a blue circle (features "blue" and "round"), and to indicate its absence or presence by a key press. The target is accompanied by a number of distractors. If the target can be discriminated from the distractors on the basis of a single attribute, the search is effortless and the target is readily detected even in a large set of distractors. For instance, the blue circle is easily seen among red circles. In this case, attention is not necessary to tie together the form and shape of the objects because the work of the color module is sufficient to signal the presence of the target. In this condition, the blue target is "salient" and will "pop out"



Perception in Vision. Figure 2 Pathways from V1, in the occipital lobes, to the temporal and parietal cortices. The dorsal pathway from V1 to the posterior parietal cortex is important for object localization and action control. The ventral pathway from V1 to the inferotemporal cortex is important for object recognition.

from the red distractors. If, however, a conjunction of attributes has to be detected, the search is more effortful. For example, it is more difficult to detect a blue circle among blue squares and red circles. According to the feature integration theory, the observer has to scan one object after another and focus attention on each individual object to determine whether the required conjunction is present. The work of a single module is not sufficient (color and form is important), such that serial, attention-demanding integration of attributes is necessary. Consequently, reaction times in a conjunction search increase with the number of distractors.

There is general consensus that attention is necessary for conscious perception to occur. In a phenomenon called “inattention blindness,” observers fail to detect large changes in a picture if their attention is diverted by a secondary task [7]. For instance, observers may fail to notice a black gorilla walking through a scene if they are asked to count the passes of a team dressed in white playing against a team dressed in black. Even if the gorilla was clearly processed at the sensory level, it failed to be consciously perceived because the observer was focusing on white elements in the scene. Thus, both high-level cognitive and low-level sensory processes determine our visual world.

References

1. Gregory RL (1997) *Eye and brain: The psychology of seeing*. Oxford University Press, Oxford, UK
2. Hubel DH, Wiesel TN (2005) *Brain and visual perception: the story of a 25-year collaboration*. Oxford University Press, Oxford, UK
3. Weiskrantz L (2004) Roots of blindsight. *Progr Brain Res* 144:229–241
4. Goodale MA, Milner D (2004) *Sight unseen*. Oxford University Press, Oxford, UK
5. Farah MJ (2004) *Visual agnosia*. MIT Press, Cambridge, MA
6. Treisman AM (1998) Feature binding, attention and object perception. *Philos Trans R Soc Lond B Biol sci* 353:1295–1306
7. Rensink RA (2002) Change detection. *Annu Rev Psychol* 53:245–277

Perception, Philosophy

ALEXANDER STAUDACHER
Otto-von-Guericke-Universitaet Magdeburg, Institut
für Philosophie, Magdeburg, Germany

Definition

In current philosophical debates on perception the term “perception” refers almost exclusively to sense

perception, although it can be used (like the French “perception” or the German “Wahrnehmung” as well) for the acquisition of knowledge in general. Commonly there are taken to be five senses: sight, hearing, smell, touch and taste. Discussions concentrate for the most part on the sense of sight, however. Although it was at one time argued that perceptual verbs like “to see,” “to hear” etc. don’t refer to a kind of mental state, episode or event, because they qualify certain observations as successful in the same vein as “to win” does not describe an event or episode but reports an achievement, it is common now to acknowledge the existence of perceptual states and to take perceptual verbs as referring to those states.

Description of the Theory

One may distinguish in the philosophy of perception basically two kinds of different issues: the first issue concerns the question of how perception as a particular mental phenomenon is to be construed. The second issue concerns epistemological questions, that is, questions dealing with the role of perception in the acquisition of factual knowledge. Making such a distinction is not to deny that both issues are connected in many ways. Indeed, it seems obvious that satisfying answers to the epistemological questions presuppose that at least some questions concerning the first issue have been settled. The main focus of this article will lie, however, on the first issue. The following questions are of particular importance: How is the representational content (henceforth simply: content) of perceptual states to be understood? Mental states in general represent the world to be a certain way; they tell us how the world is in certain respects. In this sense my perception of the tree outside the window represents the world to be a certain way. Correspondingly, there can arise two cases of misrepresentation here, illusion and hallucination. Illusions are cases where something in perception appears to be different from the way it actually is (e.g. a dummy of a tree appearing as a tree). In hallucinations objects appear to be there where no such object is present at all (e.g. the rats hallucinated by a delirious alcoholic). Accordingly, the philosophy of perception not only has to specify the nature of perceptual content (including the question as to whether or not it is similar to the content of other mental states like belief or thought) but has to give also an adequate account of illusion and hallucination. Mental states and their contents are related in various ways to one another and to our actions: we entertain beliefs with certain contents (e.g. that it will rain soon) because we have other contentful mental states (e.g. we perceive a sky full of grey and heavy clouds, we believe this to be a reliable sign of coming rain etc.) and we will therefore act in a certain way (we take our umbrella with us) and so on. This leads to the question of how perceptual content is related to other mental content and to the further question of what

kind of structure it has to possess in order to be able to stand in these relations.

A further question concerning the nature of perceptual states is whether they can be exhaustingly characterized by reference to their content. Perceptual states are often taken to be phenomenally conscious, that is, it is somehow for the perceiving subject to have them. They have a certain distinctive “feel” to them which distinguishes them from mere beliefs and thoughts. While seeing a tree I experience the colors of its leaves in a vividly conscious way which is lacking when I am merely thinking of these colors.

At a most general level one can divide theories of perception into two different classes which give different answers to the question what we have to take as the immediate objects of perceptual awareness. According to the one class we are immediately aware of the physical objects of perception, such as tables, trees, clouds and people etc. These objects are public in the sense that they can be perceived by more than one subject and they exist independently of whether someone perceives them. Furthermore, they change their properties neither when perceived under different perceptual conditions (e.g. varying perspectives or lighting-conditions) nor in the light of varying mental conditions of the perceiver which can influence her perceptions (e.g. expectations, drugs etc.). Theories belonging to the first class are generally called [▶direct realism](#).

According to the other class we are immediately aware of “[▶sense data](#).” An example of a sense datum is the more or less round, red, bulgy expanse you are immediately aware of when you are seeing a ripe tomato in normal daylight. A sense datum isn’t public in the sense that two subjects can be aware of it. Furthermore, it has been assumed that sense data cannot exist independently of our awareness of them and that they regularly change when the perceptual conditions or our mental preconditions change. If we look, for example, at the tomato under different lighting-conditions what we will be immediately aware of will be a sense datum of a different color than before. Furthermore, you will also be directly aware of sense data in cases where no physical object is present at all (hallucination) or where this object is different from the way it appears to you in perception (illusion) (see sense data).

Sense data theories have claimed that an adequate picture of our perceptual awareness in cases of hallucinations and illusions requires the assumption that we are in these cases immediately aware of sense data which instantiate the properties no physical object actually present has. Furthermore, they have tried to show that the immediate objects of our perceptual awareness in cases of veridical perception have to be sense data as well. The vividly experienced colors (felt temperatures

etc.) making up the phenomenal aspect of conscious perception can be seen according to these theories as properties of the sense data we are aware of. Concerning the question of how perceptions are related to other mental states sense data theories have traditionally assumed that perceptual states can be a secure fundament for all our empirical knowledge because we are immune against error as far as our sense data are concerned. These data will be as they appear to us. More recent defenses of sense data have put more emphasis on the role of these data in an adequate account of perceptual awareness; the epistemological presuppositions which gave rise to the search for a secure fundament of empirical knowledge have come into discredit in the last decades. There are basically two rival theories within this class, [▶indirect or representative realism](#) and a certain version of [▶phenomenalism](#). According to [▶indirect realism](#) we have to distinguish between sense data and the mind-independent physical objects of the world surrounding us. Whereas we are in perception directly or immediately aware of sense data, our perceptual awareness of physical objects is only indirect in the following way: in the case of veridical perception the physical object is the cause of the sense datum; it is the first member of the causal chain that leads via the stimulation of our senses and the ensuing processes in the brain to the occurrence of the latter. Sometimes this causal account is supplemented with the claim that sense data function as natural signs for the physical objects they are caused by. In the case of hallucinations the causal chain won’t start with the physical object; in the case of illusions the physical object will play a causal role but the chain will be influenced by further factors. Historically, this account has also been strongly motivated by the claim that physical objects don’t possess the kind of properties they seem to possess according to our perceptions of them; meaning they are, e.g. neither colored in the way they appear to our eyes nor warm or cold in the way they feel to our hands, but possess only those properties physics must postulate in order to explain their causal interaction (including the interaction with our bodies). A theory of this kind can be traced back to the writings of René Descartes (1596–1650) and John Locke (1623–1704); for more recent defenses see [2].

Given that our perception of physical objects is indirect in that indicated way it seems that our knowledge of them is also indirect. We may either conclude that physical objects are the causes of our sense data or we just believe it to be that way, but are such beliefs or conclusions justified at all? According to one of the major objections to indirect realism the answer has to be negative and consequently indirect realism can’t be justified either because one of its central claims is that physical objects are often among the causes of our sense

data. According to this objection indirect realism cannot justify this claim because information about causal relationships has to be established empirically by the observation of cause and effect. But if indirect realism is right, the only available empirical information is our immediate perceptual awareness of our sense data. Therefore, the only information we can get will be about the effect but not about the cause. Consequently, indirect realism seems to undermine itself and to lead to skepticism concerning the existence of the physical world.

A typical indirect realist answer to this challenge is to use a strategy which is familiar in the philosophy of science when it comes to justifying the existence of unobservable scientific theoretical entities like molecules, atoms and so on. It is admitted that we have no empirical access to physical objects in the strict sense but it is held that we are nevertheless justified in claiming their existence, because this claim gives us the best explanation for the fact that the sequence of our sense data possesses the order and structure it actually does [2].

Phenomenalism can be traced back to central claims of the philosophy of George Berkeley (1685–1753); for a classical defense in the twentieth century see [1]. Roughly put, phenomenalism holds that physical objects can be identified with complex sequences of actual and possible sense data, and concludes that direct awareness of these comes down to direct awareness of physical objects. A tomato is then nothing but the complex sequence of sense data I have when I am actually looking at it or I would have if I took a different perspective of it or touched it and so on. If physical objects are nothing but sequences of actual or possible sense data a claim like “There exists a rock in the desert nobody has seen so far” has to be interpreted as the claim “If you go to a certain place in the desert you will enjoy sense data of a rock.”

It has been objected to phenomenalism that our talk about existing physical objects can’t be replaced in that way by talk about actual and possible sense data. To be complete, the required interpretations would not only have to be of a kind of complexity no one has been able to arrive at so far (note, that these analyses would also have to comprise phrases like “you go to a certain place in the desert”), they seem to be at odds with the causal roles we ascribe to physical objects that no one perceives (think of the roots supporting the trunk of a tree); to be the cause of something requires that it actually exists. However, unperceived objects are according to phenomenalism only sequences of possible sense data a perceiver would have if he were in the right situation. More recent statements of phenomenalism have therefore tried to defend versions which don’t require such interpretations [4].

Direct realism has been traced back to Aristotle (384–322 B.C.), Thomas Aquinas (c. 1224–1274), and

the Scottish common sense philosopher Thomas Reid (1710–1796), although these historical ascriptions are a matter of controversy. Direct realism comes in a variety of different forms, differing are mainly as to how the content of perceptual states is best to be construed.

According to the ►[belief-theory of perception](#), perceptions are a certain kinds of beliefs we acquire with the help of our sense organs (for more qualifications as to what special kind of beliefs perceptions are see [9]). Beliefs have propositional content, that is, content which can be specified with the help of a that-clause in which something is classified in a certain respect with the help of a concept (e.g. “Peter believes that grass is green”). The possession of concepts (“grass,” “green”) implies among other things at least the ability of the believer to recognize things as being able to under that concept. This proposal accords well with the fact that we often express the content of perceptions with the help of that-clauses and imply the possession of the relevant concepts by the perceiver when we say things like “Sarah sees that there is milk left in the fridge.” It can also explain how perceptions serve to justify other beliefs (Sarah’s belief that she doesn’t have to go the super-market now), because justification proceeds by inferences and inferential relations can be explained best by reference to a content with propositional structure.

Nevertheless, this account faces serious difficulties: Sometimes the content of our perceptions can’t be equated with the contents of our beliefs: we may perceive the arrows of the well known Müller-Lyer figure to be of a different length, although we know quite well that they are in fact of the same length. Although we modify our beliefs in the light of new beliefs, our perceptions often aren’t accessible to this kind of revision. Perception in contrast to beliefs seems to be, as it is called, “modular” (for more on modularity see [6]). With their equation of perception to belief and thought belief-theories have notorious difficulties in doing justice to the fact that perceptions are phenomenally conscious. In order to avoid the introduction of sense data at this point the so-called ►[adverbial theory of experience](#) has held that the phenomenal aspect of our sense experiences can be analyzed in the following way: a vivid conscious experience of something red (be it veridical or not) can be understood as a certain way of perceiving; that is, we are not conscious of something instantiating the property which is responsible for the character of our conscious experience (a sense datum), but our perceptual state itself is characterized by that property, in the case of an experience as of something red we “sense in a redly manner”, as it has been put [7]. It has been claimed, however, that this account cannot deal adequately with situations where we have an awareness of a manifold of different items with different colors and forms because this requires

being aware of different items instantiating these properties [2]. An alternative account that may be able to deal with the problems of the belief-theory is ►representationalism (not to be confounded with representative or indirect realism) [8]. Representationalism seems especially apt to avoid a third problem of the belief-theory, the fact that we can also perceive things without disposing of the relevant concepts; or, as it is often put, that perception can have nonconceptual content. We not only render the content of perceptions with the help of that-clauses, but by saying also things like “He sees the computer” or “He heard the Tristan-accord.” With statements like these we often don’t imply that the perceiving subject has to have the concept of a computer or of the Tristan-accord in order to see or hear these things (think of a baby or a dog as the perceiving subjects). According to representationalism we have non-conceptual perceptual representations of the items in question. The admission of the existence nonconceptual content leads to the question of how this kind of content is related to conceptual content and how it can play a role in the justification of our empirical beliefs. Here it has been argued that perceptual content can fulfill its role in the justification of empirical beliefs only if it is taken to be conceptual, which means that the representationalist claim concerning the nonconceptual character of our perceptual experience finally can’t be right [9]. Whether this objection is sound is a matter of ongoing discussions.

Representationalism also uses the idea that perceptions have nonconceptual content in order to explain the fact that perceptions are phenomenally conscious. To put it very roughly, phenomenally conscious states are conceived as nonconceptual representations which deliver information to the perceiver he which can use to form his beliefs and desires. These states acquire their nonconceptual content by being dependent in the right way on the features they represent (e.g. they are caused by them under optimal conditions; therefore the presence of red objects leads in general to perceptions of red). Because the typical phenomenal aspects of our sense experiences are experienced by the perceiver as features of the represented surroundings (e.g. in a conscious perception of the blue sky the blue is experienced as a feature of the sky), representationalism claims that perceptual states acquire their phenomenal character by being related in the right way to certain features of our surroundings: we represent the blue of the sky in a nonconceptual way. Whether such a conception of the nonconceptual content of perception can be used to explain the phenomenally conscious aspect of perception is, however, also a matter of controversy [1].

All positions considered so far share the presupposition that veridical perceptions and hallucinations have something in common. In both cases the perceiver

will either have sense data, or perceptual beliefs, or nonconceptual representations or states that can be characterized by an adverbial modification. There is, however with the so-called “►disjunctive account” of sense experience [10] a further variety of direct realism which puts this presupposition in question: according to this position a perceptual experience is either a perception or a hallucination (a disjunction of these two types of states), but these two types of states need not share a common element: perception implies that we are aware of physical objects and the content is just constituted by the perceived aspect of the physical object itself, hallucinations however don’t imply this because there is no such object present. In the case of hallucinations we simply take ourselves to perceive something although it isn’t the case.

One consequence of this position which might be hard to swallow is that it demands that we are in the case of hallucinations not only in error about the physical world but also about the conscious mental states we are in; we assume that we are perceiving while we aren’t. A second problem is that the disjunctive account has difficulties with the fact that hallucinations and veridical perceptions are the causal consequences of the same type of brain states; one may evoke a hallucination by a stimulation of those parts of the brain which are also activated in the case of veridical perception. However according to a widely held principle on causation the same kinds of causes lead to the same kind of effects. It seems, therefore, that the adherent of the disjunctive account has to give up this principle, because according to his account there is nothing in common between hallucinations and veridical perceptions even though they result from the same kind of brain stimulation (for further discussion see [4]).

References

1. Maund B (2003) Perception. McGill-Queen’s University Press, Montreal
2. Jackson F (1977) Perception. A representative theory. Cambridge University Press, Cambridge
3. Ayer AJ (1940) The Foundations of empirical knowledge. Macmillan and Co., London
4. Robinson H (1994) Perception. Routledge, London
5. Pitcher G (1971) A theory of perception. Princeton University Press, Princeton
6. Fodor J (1983) The modularity of the mind. MIT Press, Cambridge/Mass
7. Chisholm R (1957) Perceiving: a philosophical study. Cornell University Press, Ithaca/NY
8. Tye M (1995) Ten problems of consciousness. MIT Press, Cambridge/Mass
9. McDowell J (1994) Mind and world. Harvard University Press, Cambridge/Mass
10. Haddock A, Macpherson F (ed.) (2007) Disjunctivism: Perception, Action, Knowledge. Oxford University Press, Oxford

Perceptive Field

Definition

Psychophysical counterpart of receptive field organization.

Term first introduced by Jung and Spillmann (1970) to link perceptual properties to neuronal function. Although psychophysical data represent the final stage of integration of the activity of numerous neurons, they typically resemble those obtained with single cell recordings (single neuron doctrine by Barlow 1972). Perceptive fields may thus be regarded as psychophysical equivalents of receptive fields with their various forms of center-surround antagonism and selective spatio-temporal sampling characteristics that allows for non-additive, Gestalt-like integration of the stimulus input.

► [Psychophysics](#)

Perceptron

Definition

The Perceptron was the first neurocomputer (artificial neural network) to be developed. The original Perceptron consisted of two layers of units (input and output layer) and used a simple learning rule for weight adjustment according to the difference of the network output and the target vector. It is capable of solving linearly separable problems. It can be proven that the network converges to a solution (i.e., reaches its error minimum) within a finite number of steps for any linearly separable problem. Multilayer Perceptrons with hidden (intermediate) layers of units are more powerful and can learn complex non-linearly separable problems.

► [Connectionism](#)
 ► [Neural Networks](#)

Perceptual Completion

► [Perceptual Filling-In](#)

Perceptual Constancy (in Vision)

Definition

The tendency of perceiving objects and scenes as being invariant in size, shape, lightness, color, etc., despite variation of sensory inputs originating in the same objects and scenes observed from varying viewing distance, at varying viewing angle, in varying illumination, etc.

► [Color Constancy](#)

Perceptual Correlates

► [Visual Neuropsychology](#)

Perceptual Discrimination

Definition

Ability to distinguish between different levels of a perceptual dimension such as color, pitch, or pressure.

The perceptual dimension may map directly onto a physical dimension (e.g. the perceived length of a bar may also be measured) or may be created by the perceptual system (e.g. we perceive colors but the rays of light are not colored).

► [Perceptual Impairment](#)
 ► [Perception](#)

Perceptual Filling-In

IKUYA MURAKAMI

Department of Life Sciences, University of Tokyo,
 Tokyo, Japan

Synonyms

Perceptual completion

Definition

Perceptual filling-in refers to the visual phenomenon in which a certain part of the ► [visual field](#) appears to be

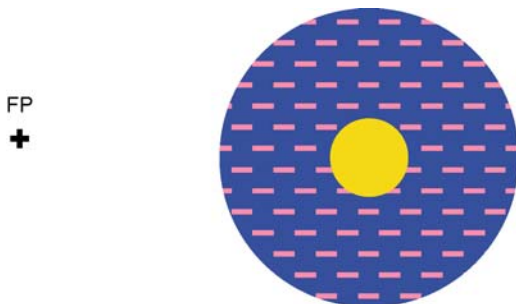
overwhelmed or filled with the visual attributes, such as brightness, color, and texture, of the surrounding area. Filling-in connotes planar interpolation of surface properties; linear interpolation of contour and bar is often referred to as perceptual completion. Though filling-in at the ►**blind spot** has been studied most extensively, mechanisms of perceptual filling-in are considered to be rather ubiquitous in the normal visual field as well.

Characteristics

Phenomenal Variations

Since vision is a process of ecologically valid estimation of our outer world, our visual system has evolved so as to infer object properties from impoverished visual inputs on the ►**retina**. As a result, in a great variety of situations the brain assumes a surface to be filled with color and texture from outside, especially when retinal inputs to that surface part are unavailable or poor.

One of the most striking examples is filling-in at the blind spot, an oval-shaped area (approximately 5 degrees in diameter) defined for each eye, located at approximately 15 degrees horizontally from the center of the visual field. This area is insensitive to light stimulation because ►**photoreceptors** are totally absent at the corresponding retinal region (optic disc). Why does this visual deficit go unnoticed? As the blind spot of one eye is a normal field of view for the fellow eye, a complete visual scene is of course available with both eyes open. However, the visual world also seems as complete with only one eye open. Clearly, perceptual filling-in is constantly at work there. One can easily convince oneself of this phenomenon by looking at an annular shape fully covering the border of the blind spot (Fig. 1): the annulus appears to be a large solid disk uniformly filled with the color and texture of the figure.



Perceptual Filling-In. Figure 1 Perceptual filling-in at the blind spot. As the annulus covers the border of the blind spot of the right eye, the yellow inner disk perceptually disappears; the inside appears to be filled with the same color and texture as in the annulus. The reader can experience filling-in by looking straight at the fixation point labeled “FP” with only the right eye open, from an appropriate viewing distance.

Perceptual filling-in can also occur at a small deficit (►**scotoma**) of the visual field that arises for a few people from an acquired local damage to the retina (or other visual pathways). This might explain why patients with local ►**retinal degenerations** are sometimes unaware of their scotoma before they take ophthalmologic testing across the visual field. The monkey has also been shown to see perceptual filling-in both at the natural blind spot and at a scotoma caused by retinal damage [1].

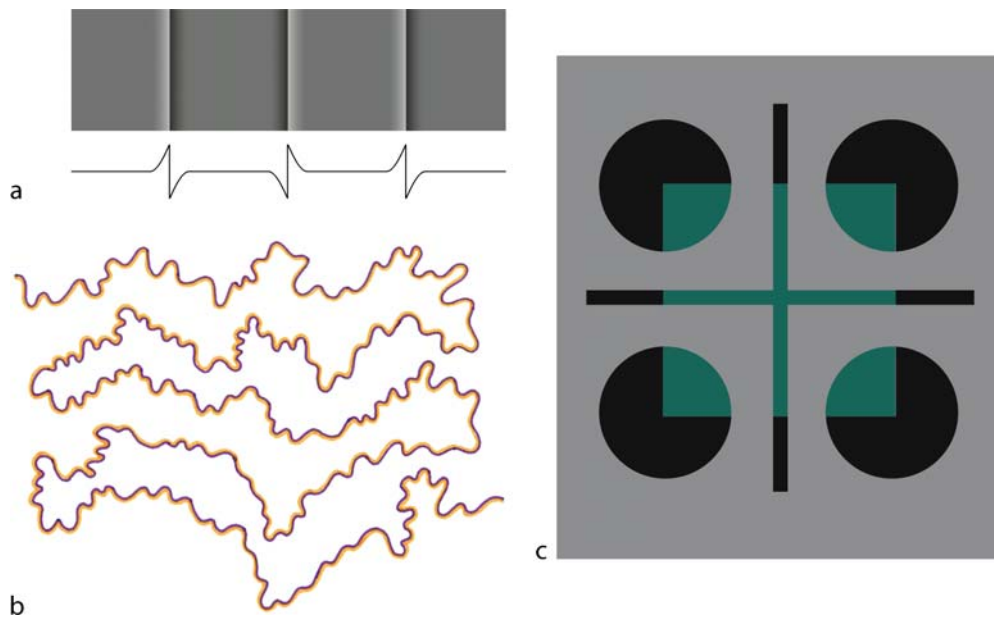
Whereas perceptual filling-in at the blind spot and scotoma occurs in the region without visual inputs, filling-in also occurs in the region without visual-input *changes*. When an image is artificially stabilized on just the same part of the retina by using a special experimental device, this image is initially visible but soon fades away from one’s ►**perception**, filled-in with its background color. Normally, incessant ►**fixational eye movements** produce tiny wobbling of retinal images, preventing such perceptual fading of stationary things in everyday life. Nevertheless, by looking sideways at a faint or blurry stationary figure on a uniform background for a long time, one may experience similar image fading and filling-in with background color (►**Troxler effect**). Likewise, when one looks sideways at a stationary surface stimulus on a background of randomly twinkling texture, this surface gradually disappears from perception, filled-in with similar random twinkles of texture (►**artificial scotoma**) [2].

Other phenomena of perceptual filling-in in normal observations include the ►**Craik-O’Brien-Cornsweet effect** (Fig. 2a) and the ►**watercolor illusion** (Fig. 2b).

In these illusions, different surface parts physically share identical luminance and chromaticity, but they are perceived to have different colors when there are sharp ►**contrasts** of luminance and chromaticity at the very boundary [3]. In these cases, clear physical edges delineate one area to fill-in with one color and another area with another color. Interestingly, however, perceptual filling-in of surface can also be bounded by contours that are perceptually completed themselves (Fig. 2c). In a figure designed to induce an ►**illusory contour**, the color of certain parts of the figure perceptually fills-in the inside of the subjective square of the illusory contour but not beyond (►**neon-color spreading effect**). Altogether, these phenomena may be viewed as examples demonstrating that the visual system infers surface properties of featureless areas by using conspicuous cues nearby.

Models

How are such ►**percepts** of filling-in accomplished? To the extent that the phenomenal variety is diverse, there may exist as many theories for the mechanisms underlying them. Of these, three influential ideas have been proposed for perceptual filling-in at the blind spot and other poor regions [4].



Perceptual Filling-In. Figure 2 Various filling-in phenomena. (a) The Craik-O'Brien-Cornsweet effect. The inset indicates luminance as a function of horizontal position. The area just to the left of the central edge appears uniformly darker than adjacent areas, although the luminance changes are confined within the borders between areas. (b) Watercolor illusion. The two areas delineated by the wiggly borders appear to be filled uniformly with faint yellowish and bluish colors, although the color changes are confined within the borders, with the remaining areas left achromatic, in reality. Adapted from [3], with kind permission from the author. (c), Neon-color spreading effect. A square-shaped illusory contour is formed by the black inducers, and a bluish translucent color appears to be spreading inside the subjective square seen in front.

1. *Isomorphism.* When perceptual filling-in occurs, a two-dimensional neural map (or [▶visual topography](#)) representing that location of the visual field is actually activated as such, so that individual neurons within that map are actually excited in some fashion parallel with perceived surface properties.
2. *Symbolic Labeling.* Attributes inside a poor region can be cognitively designated by symbolic or logical operations using reliable information nearby, without invoking isomorphic activation – the brain is not “filling in but finding out” the missing surface properties.
3. *Ignorance.* One does not see a black hole of the blind spot simply because one is only aware of visual events that are abundant in the surround and “ignores the absence.”

Some recent findings have been more or less in favor of isomorphism, as we will see below, although labeling and ignorance may operate at crucial processing stages for one's [▶conscious perception](#) and [▶awareness](#).

Neurophysiological Studies

In the brain, visual signals from the retina are registered in visual topography, or a two-dimensional map of neurons topographically representing the visual field.

Are the neural representations of the blind spot and scotoma on this topography really activated when perceptual filling-in occurs? Physiologists are still on their way to solving this important question.

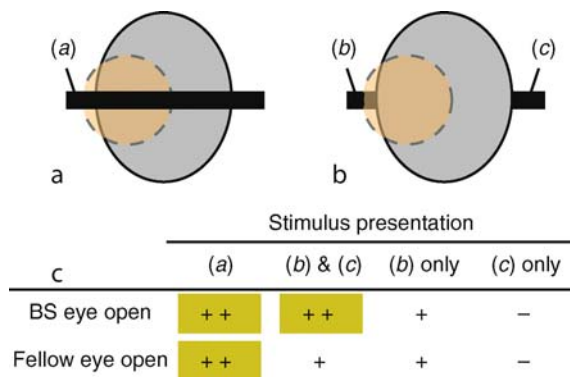
Perhaps the simplest way of neural activation would be to distort the map itself (often called the “[▶sewn-up](#)” model). The representation of the blind spot could “see” its surroundings if it received direct innervations from retinal portions surrounding the blind spot. However, current studies of functional anatomy have indicated quite orderly mapping from retina to [▶striate cortex](#) without distortion at the blind spot, and at the scotoma as well [5]. Nonetheless, some [▶single-unit recording](#) studies have suggested re-mapping of visual topography of a scotoma [6]. This scotoma was induced in an animal by producing small local lesions in the retinae. After the damage, cortical neurons that had originally coded positions inside the scotoma expanded and shifted their [▶receptive fields](#) towards the outside – as if they abandoned the damaged part and started to look out. Thus, some [▶cortical plasticity](#) might be initiated in certain conditions for adaptive compensation for retinal damage.

Besides the feedforward mapping, there are at least a couple of hypothetical schemes to make neural filling-in possible in early visual cortex. The first is lateral

propagation of visual signals into the cortical representation of the blind-spot region via horizontal connections. The second is feedback from ►extrastratial visual cortex back to early visual cortex. Yet another scenario would be that the neural correlate of filling-in resides not in early visual cortex containing neurons with tiny receptive fields, but in higher cortical areas where neurons have larger receptive fields covering the blind spot and beyond. More research is needed to determine which is the case.

A few attempts have been made to seek activities of individual neurons that parallel the filling-in phenomenon. One of the most recent findings is about the neuronal activity in striate cortex (►primary visual cortex, ►V1) of a behaving monkey (Fig. 3) [7].

These neurons had receptive fields largely overlapping the blind spot of one eye, i.e., with the other eye open, the neurons were excited by visual stimuli presented in these fields. The blind-spot eye only was open. A small bar stimulus (labeled *b*) on one side of the blind spot fell onto the tip of the receptive field, and thus caused mild firing responses as expected. Interestingly, responses increased when another bar stimulus (labeled *c*) was added on the other side, so as



Perceptual Filling-In. Figure 3 Perceptual completion at the blind spot and neuronal responses [7].

(a) Schematic illustration of the stimulus. The receptive field (broken circle) of the recorded neuron partially overlapped the blind spot (solid oval). A horizontal bar (a) was presented such that it should penetrate both the receptive field and the blind spot. (b) In other cases, the retinal input was confined within a small sub-region (b and/or c). (c) Schematic diagram illustrating responses of a few V1 neurons exhibiting increased activities during perceptual filling-in. The neuronal responses were recorded during four types of stimulus presentations while either the blind-spot eye (BS eye) only or the fellow eye only was opened. The symbols “++,” “+,” and “-” indicate strong, weak, and no responses, respectively. The yellow boxes indicate the viewing conditions in which the monkey would perceive a long bar across the blind spot.

to induce perceptual completion of a single bar across. The second bar stimulus per se did not cover the receptive field, but the perceptually completed bar did. In contrast, such a response increase was not observed with the fellow eye only open. Therefore, these neurons fired vigorously when the filled-in bar coincided with their receptive fields inside the blind spot.

The neural correlate of the “artificial scotoma” (see above) has also been investigated in the awake monkey [8]. A static, gray square was located to cover the receptive field of the recorded neuron, and the background was filled with twinkling random noise (Fig. 4a). Over prolonged observation, the static square was perceptually replaced with twinkling noise at some time. The firing activities of neurons in a higher visual area, ►V3, were initially weak but became stronger just at the time this “artificial scotoma” would be perceptually filled-in with noise (Fig. 4b).

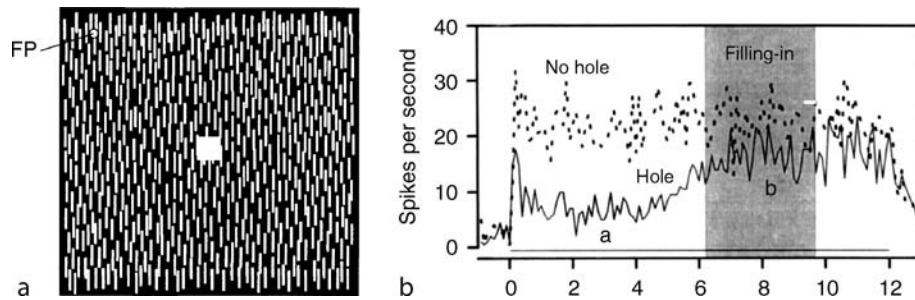
These findings seem consistent with isomorphic activations in the two-dimensional cortical map of the visual field during perceptual filling-in. Meanwhile, other studies indicate mixed results among different types of neurons, cortical areas, methodologies, and types of filling-in phenomena. At present, many important questions yet remain to be answered: what kinds of isomorphic activations of visual neurons are necessary and sufficient, how these could be implemented in a biologically feasible manner, and whether only one kind of architecture is enough for all kinds of filling-in to occur.

Perceptual Studies

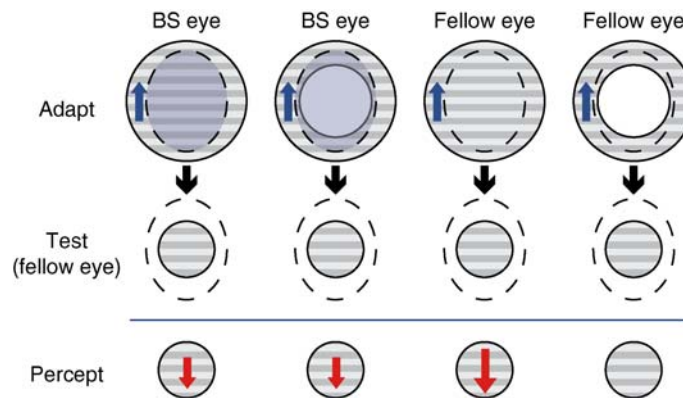
Other lines of evidence for explicit representations corresponding to perceptual filling-in come from ►psychophysics of ►visual illusions. In one such study, a phenomenon of ►motion aftereffect was used (Fig. 5) [9].

After prolonged viewing of a moving stimulus, a static stimulus presented at the adapted location appears to move in the opposite direction, and this effect is known to transfer between eyes if different eyes are used in adaptation and subsequent test. The observer was adapted to a moving stimulus covering the blind spot of one eye and thus perceptually filling-in the inside of it. Later, the stimulus was abruptly switched to a smaller static stimulus well inside the blind spot of the adapted eye, but as it was now given to the fellow eye, the observer could see it. It was perceived to move in the opposite direction to the adapting stimulus, thus the motion aftereffect was elicited after adaptation to motion filling-in inside the blind spot without direct stimulation. This finding suggests that filled-in motion and actual motion share a common pathway.

Another observation of brightness filling-in suggests topographic representation (Fig. 6) [10]. Presented on a white background was a uniformly lit disk-shaped figure, whose luminance decreased continuously from white



Perceptual Filling-In. Figure 4 “Artificial scotoma” and neuronal responses [8]. (a) Schematic illustration of the stimulus, which consisted of randomly positioned bars and a gray square covering the receptive field of the recorded neuron. Three such random-bar patterns alternated at 20 Hz. The monkey was rewarded for maintaining fixation at the fixation point (FP). (b) Typical responses from a single neuron in area V3. The firing rate is plotted against time after stimulus onset. The neuron initially exhibited a transient response to the stimulus onset followed by a low firing rate (labeled “Hole”). With prolonged observation, however, the neuron’s responses gradually increased, reaching a plateau (labeled “Filling-in”) at the time observers would experience perceptual filling-in of the square with random bars. The plateau was comparable to the firing rate of the same neuron to the same stimulus without the gray square (labeled “No-hole”). Adapted from [8], with kind permission from Nature Publishing Group.

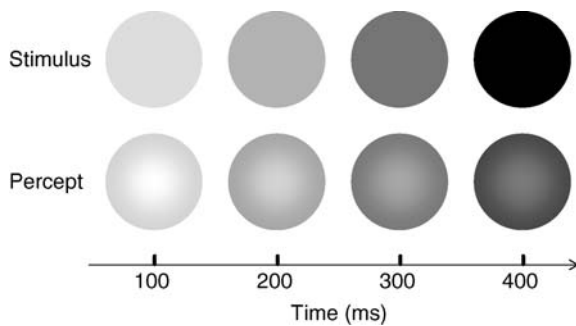


Perceptual Filling-In. Figure 5 Perceptual filling-in of motion and a subsequent motion aftereffect inside the blind spot [9]. The adapting stimulus was a horizontal grating drifting vertically (its direction is indicated by the blue arrows). The stimulus region was either a disk covering the entire blind spot (broken oval) or an annulus covering the border of the blind spot. The observer was adapted with only the blind-spot eye (BS eye) or only the fellow eye open. Note that the disk and annulus were equivalent for the BS eye. The test stimulus was a stationary horizontal grating well inside the blind spot, delivered to the fellow eye. A motion aftereffect occurred (its direction indicated by the red arrows) where motion had been perceptually filled-in during adaptation.

to black in half a second. The observer saw it darkening continuously, but its brightness was perceived as inhomogeneous: the brightness change towards the center of the disk appeared to lag behind the change at its edge. In other words, the center appeared brighter than the edge at each time slice, and darkness “swept” inward. This phenomenon could be seen in a disk placed in a normal visual field and in the same disk covering the blind spot just as well, either with the blind-spot eye or the fellow eye open. This effect appears to corroborate the propagation of brightness signals from edge to interior on the cortical map, suggesting that neural filling-in operations obey the same principle all around the visual field.

Functional Significance

The retinal image is a two-dimensional array of “raw” light intensity. From this image, the visual system has to estimate lots of things, such as object contours, surface assignment to objects, their volumetric structures, and their material properties, just to list a few. On the other hand, retinal inputs never provide the brain with sufficient information for solving these problems. For example, the brain has to determine what surface is lit by what light source, but the retinal image is only a result of their interactions. Thus, the same surface can project very different images onto the retina depending on viewing conditions. Also, the image of the same surface under the same illumination may be registered



Perceptual Filling-In. Figure 6 Brightness filling-in in a normal visual field [10]. On a computer monitor, a small spot of light (1 degree in diameter) gradually changed its luminance from white to black over time. Its perceived brightness was different between the edge and inside: the brightness at the edge appears to fill inward. The same phenomenon occurs at the blind spot as well, with a larger spot of light (8–10 degrees in diameter).

as having different values of chromaticity, because of differences in our spectral sensitivity across space and time. Furthermore, the same surface may even be partially unregistered (blind spot and scotoma). Therefore, filling-in has a clear functional significance of maintaining our [▶perceptual constancy](#) in spite of imperfection of visual information from the eye. As perceptual filling-in is viewed this generic way, a great number of puzzles remain to be solved in future research.

References

1. Komatsu H (2006) The neural mechanisms of perceptual filling-in. *Nat Rev Neurosci* 7:220–231
2. Ramachandran VS, Gregory RL (1991) Perceptual filling in of artificially induced scotomas in human vision. *Nature* 350:699–702
3. Pinna B, Brelstaff G, Spillmann L (2001) Surface color from boundaries: a new ‘watercolor’ illusion. *Vision Res* 41:2669–2676
4. Pessoa L, Thompson E, Noë A (1998) Finding out about filling in: a guide to perceptual completion for visual science and the philosophy of perception. *Behav Brain Sci* 21:723–748
5. Smirnakis SM, Brewer AA, Schmid MC, Tolias AS, Schüz A, Augath M, Inhoffen W, Wandell BA, Logothetis NK (2005) Lack of long-term cortical reorganization after macaque retinal lesions. *Nature* 435:300–306
6. Gilbert CD, Wiesel TN (1992) Receptive field dynamics in adult primary visual cortex. *Nature* 356:150–152
7. Matsumoto M, Komatsu H (2005) Neural responses in the macaque V1 to bar stimuli with various lengths presented on the blind spot. *J Neurophysiol* 93:2374–2387
8. De Weerd P, Gattass R, Desimone R, Ungerleider LG (1995) Responses of cells in monkey visual cortex during perceptual filling-in of an artificial scotoma. *Nature* 377:731–734

9. Murakami I (1995) Motion aftereffect after monocular adaptation to filled-in motion at the blind spot. *Vision Res* 35:1041–1045
10. Paradiso MA, Hahn S (1996) Filling-in percepts produced by luminance modulation. *Vision Res* 36:2657–2663

Perceptual Grouping

Definition

▶ [Form Perception](#)

Perceptual Impairment

Definition

Inability to distinguish between different levels of a perceptual dimension such as color, pitch, or pressure.

The impairment may originate at a peripheral level (e.g. absence of a particular cone type in the retina leads to color blindness) or at a central level (e.g. lesions of a cortical region). The impairment may regard particular regions of space, particular perceptual dimensions (e.g. color, movement, etc.) or the recognition of what is perceived (e.g. inability to recognize familiar faces).

▶ [Perceptual Discrimination](#)

▶ [Perception](#)

Perceptual Processing

▶ [Visual Neuropsychology](#)

Perceptual Saliency (in Vision)

Definition

Degree to which a target stimulus “pops out” in a set of stimuli. If the target stimulus differs by a single attribute (e.g. its color) from the other objects, it is highly salient.

If the target stimulus differs by a combination of attributes (e.g. a combination of color and form) from the others, it is less salient.

► **Perception**

Perceptual Task

Definition

Detection or classification of a stimulus or discrimination between different stimuli.

► **Sensory Plasticity and Perceptual Learning**

Perforated Patch

Definition

A form of patch-clamp recording in which an antibiotic such as nystatin, amphotericin, or gramicidin are included in the patch solution to create ionophores in the plasma membrane that permit intracellular recording without modifying the cytosolic contents of the neuron.

► **Patch Clamp**

Perforated Synapse

DANIEL A. NICHOLSON, YURI GEINISMAN
Department of Cell and Molecular Biology,
Northwestern University's Feinberg School of
Medicine and Institute of Neuroscience, East Chicago
Avenue, Chicago, IL, USA

Synonyms

Synapse with a perforated or discontinuous postsynaptic density (PSD); Synapse with subsynaptic plate perforations; Synapse with a fenestrated, Horseshoe-shaped or segmented PSD; Synapse with an annulate, Horseshoe-shaped or multifocal presynaptic vesicular grid

Definition

► **Perforated synapses** belong to a special morphological variety of synaptic junctions, characterized by the presence of aligned discontinuities (gaps) in their postsynaptic and presynaptic densities.

Characteristics

Quantitative Description

Ultrastructural features of perforated synapses, their quantitative characteristics and changes under various experimental conditions were the subject of numerous investigations. The results of these studies, which were previously reviewed in detail [1–5], are summarized below.

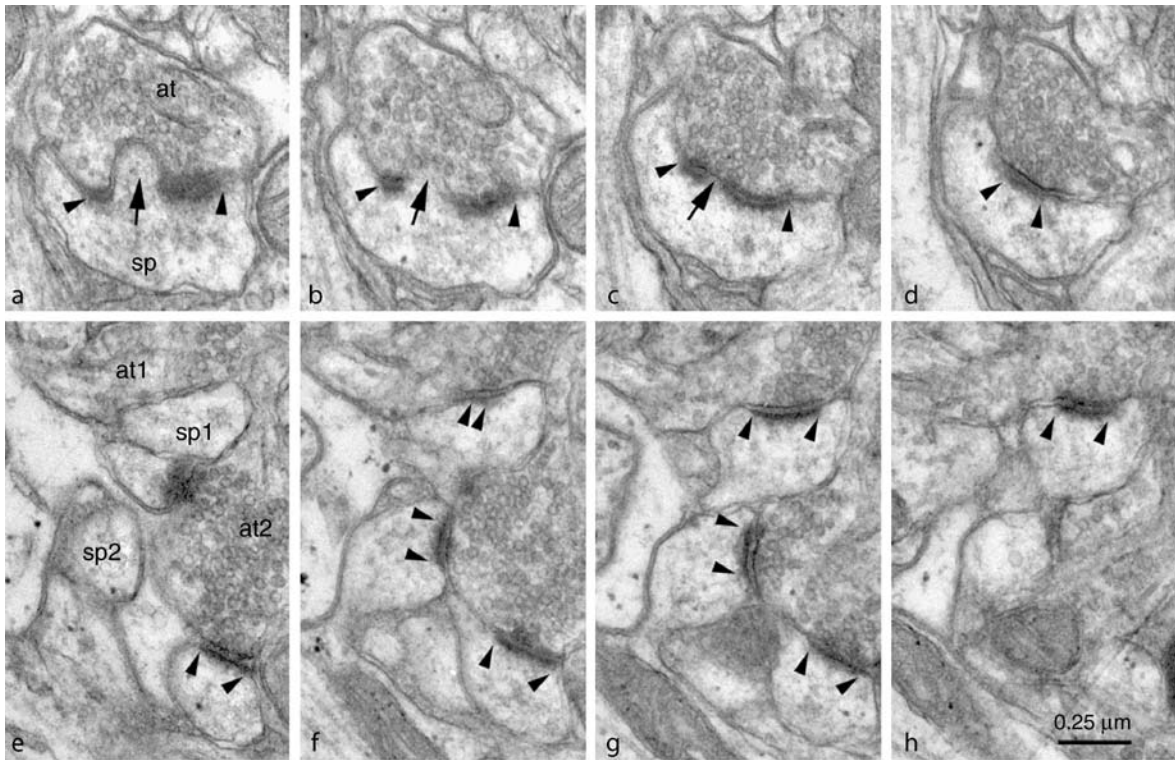
Ultrastructure

The hallmark of a synapse at the electron microscopic level is the ► **postsynaptic density** (PSD). The PSD is a plate(s) of electron-dense material on the cytoplasmic face of the postsynaptic membrane. PSDs are most noticeable in ultra thin sections of tissue conventionally prepared (i.e., osmicated) for electron microscopy (Fig. 1).

Synapses can be subdivided based on the thickness of their PSD, relative to that of the ► **presynaptic density**, into two main types: asymmetric synaptic junctions with a thicker PSD are considered to be excitatory; and symmetric ones with a PSD nearly as thin as the presynaptic density are considered to be inhibitory. Electron microscopic analyses of asymmetric synapses have demonstrated that they can be further subdivided, based on the configuration of their PSDs into either perforated or nonperforated (or macular) ones. When sections are made perpendicular or at an angle to a perforated PSD, a discontinuity or perforation is usually observed in a subset of its sectional profiles (Fig. 1a–c). Perforated PSD shapes can also be visualized in sections passing parallel to PSDs. Planar reconstructions of perforated PSDs from consecutive serial sections show that they assume three basic shapes: a fenestrated PSD exhibiting a hole(s) in its single plate; a horseshoe-shaped PSD having a single plate; and a segmented PSD consisting of several (2–4) separate plates. ► **Nonperforated synapses**, on the contrary, are characterized by a continuous PSD plate of a relatively simple shape, which may be approximated by that of a circular or elliptical disk. Sectioning of such a plate at different angles produces PSD profiles that lack perforations (Fig. 1e–h). Although dimensions of nonperforated PSDs are generally smaller than those of perforated ones, this is not an invariant feature of nonperforated PSDs because some of them overlap in size with perforated PSDs.

Distribution

Perforated synapses are widely distributed throughout the mammalian brain, including various neocortical areas, the hippocampal formation, striatum, putamen,



Perforated Synapse. Figure 1 Perforated (a–d) and nonperforated (e–h) axospinous synapses, seen in electron micrographs of consecutive serial sections through the middle molecular layer of rat dentate gyrus. (a–d) The perforated synapse (its presynaptic axon terminal and postsynaptic spine head are labeled in (a) by “at” and “sp,” respectively) exhibits PSD profiles (arrowheads) that have a discontinuity (arrowheads) in some sections (a–c). A synaptic spinule (a, b) is a finger-like protrusion of the spine head, which invaginates through a discontinuity in the PSD (arrows in a and b) into the axon terminal. (e–h), The nonperforated synapses formed between axon terminals (labeled in (e) by “at1” and “at2”) and spine heads (labeled in e by “sp1,” “sp2” and “sp3”) display continuous PSD profiles (arrowheads) in all sections.

deep cerebellar nuclei, and hypothalamus. Both perforated and nonperforated **▶asymmetrical synapses** are found mainly on dendritic spines and occasionally on dendrites. Axospinous perforated synapses have been extensively studied, and the present essay is focused on these synaptic junctions, which will be referred to as perforated synapses.

Frequency

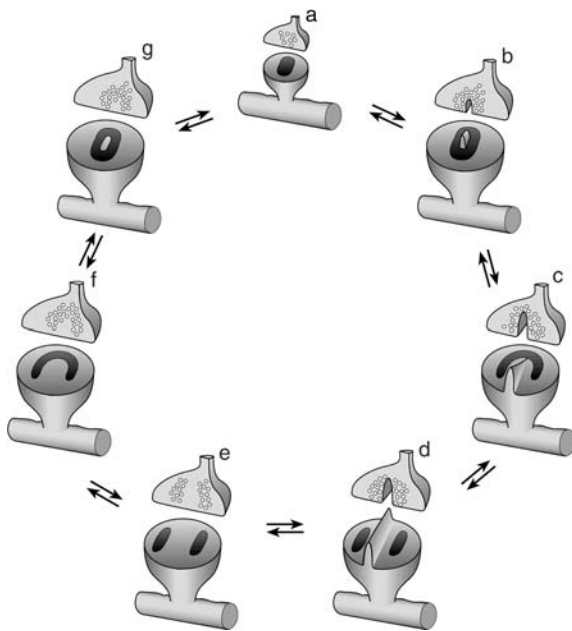
Perforated synapses constitute 10–25% of the entire axospinous synaptic population. Nevertheless, the number of perforated synapses per neuron is substantial. For example, the total number of pyramidal neurons in rat CA1 hippocampal region is ~400,000, whereas the total number of perforated synapses in one of its layers (stratum radiatum) reaches ~800,000,000. Therefore, each CA1 pyramidal neuron receives ~2,000 perforated synapses in the stratum radiatum alone.

Lower Level Components

A **▶synaptic spinule or spine partition** is a postsynaptic component of some perforated synapses. In single

sections, it is seen as a small outgrowth that arises from the spine head at a PSD discontinuity and protrudes into the presynaptic axon terminal (Fig. 1a, b). Three-dimensional reconstructions of perforated synapses demonstrate that the extent of spinules differs depending on the shape of perforated PSDs [2]. In fenestrated synapses, they assume the form of a focal partition, the base of which is limited to a hole in the PSD plate (Fig. 2b).

Horseshoe-shaped synapses exhibit a spinule whose base is restricted to the interval between the two arms of the PSD horseshoe (Fig. 2c). In segmented synapses, however, a complete spine partition divides the spine head cavity into separate compartments, each one containing a discrete transmission zone between the axon terminal and a PSD segment (Fig. 2d). Each perforated synaptic subtype can have or lack spine partitions (Fig. 2e–g). In the molecular layer of rat dentate gyrus, the proportion of synaptic junctions with partitions in total samples of fenestrated, horseshoe-shaped and segmented synapses amounts to 38, 60 and 92%, respectively.



Perforated Synapse. Figure 2 Diagram illustrating a hypothetical synapse restructuring that may underlie activity-dependent alterations in synaptic strength. The schematic shows the following axospinous synaptic subtypes: nonperforated synapse (a) perforated synapses that have a fenestrated PSD and focal spine partition (b) a horseshoe-shaped PSD and sectional partition (c) a segmented PSD and complete partition (d) or that lack spine partitions but exhibit a segmented (e) horseshoe-shaped (f) and fenestrated (g) PSD. The sequence of synapse remodeling from a through to b, and c to d is postulated to be a rapid process that supports an initial maximal synaptic enhancement. The sequence from d through to e, f and g to a may lead to the return of elevated synaptic responses to the control level.

► **AMPA receptors and NMDA receptors** (AMPA and NMDARs, respectively) are types of ionotropic glutamate receptors associated with the PSD of excitatory synapses. These PSDs also contain cytoskeletal scaffolding and adaptor proteins as well as signaling molecules, which together form a cluster of synaptic signal transduction machinery located at or near the site of synaptic transmission. Compelling electrophysiological evidence indicates that the number of postsynaptic AMPARs and NMDARs is the major determinant of synaptic strength. ► **Postembedding immunogold electron microscopy** reveals striking differences in the expression of AMPARs and NMDARs between perforated and nonperforated axospinous synapses, which may indicate corresponding differences in the strength of synaptic transmission at these synaptic subtypes [6,7]. Interestingly, some nonperforated synapses exhibit NMDAR but not AMPAR immunoreactivity, whereas

perforated synapses are invariably immunostained for both receptor types. This finding may mean that perforated synapses are never postsynaptically “silent” at resting membrane potentials. Moreover, perforated synapses from rat CA1 stratum radiatum express significantly more AMPARs (by 660%) and NMDARs (by 80%) than their immunopositive nonperforated counterparts. The total area of the PSD plate(s) is generally larger in perforated synapses as compared to nonperforated ones, and postsynaptic AMPAR content positively correlates with PSD size. The difference in the expression of glutamate receptors between the two synaptic subtypes remains significant, however, when their PSD areas are equalized, indicating that this difference is related to both PSD configuration and PSD size.

Function

Numerous studies report activity-dependent increases in the number or proportion of perforated synapses. Such changes occur in cortical regions of the rodent brain during postnatal development and under various experimental conditions including housing of animals in complex environments, hippocampal kindling, NMDA-dependent hippocampal LTP and behavioral learning. Based on these observations, perforated synapses have been widely implicated in synaptic plasticity. It is necessary, however, to note here that many of the reported results should be considered with caution. The majority of studies published so far employed inappropriate procedures for quantification of perforated synapses. For example, in studies that analyzed synapses on single (rather than consecutive serial) sections, perforated synapses might not have been reliably recognized and quantified because they frequently exhibit nonperforated PSD profiles (Fig. 1b).

Such methodological drawbacks notwithstanding, there is a growing body of evidence in favor of the long-standing notion that an addition of perforated synapses is required to support an enhancement of synaptic strength. Especially demonstrative in this respect are the findings of LTP experiments [8,9], showing that perforated synapse number is markedly increased early (15–60 min) after LTP induction, when synaptic responses are maximally enhanced, and returns to control levels afterwards. The observed increase in the proportion of perforated synapses reflects a selective change in the number of segmented, completely partitioned synaptic junctions [8,9].

The existence of distinct morphological subtypes of axospinous synapses suggests a hypothetical model [2,4] of structural synaptic modifications associated with activity-induced alterations of synaptic strength (Fig. 2). According to this model, LTP induction triggers an enlargement of nonperforated PSDs, which is followed by the consecutive formation of perforated

synapses having initially a focal spine partition with a fenestrated PSD (Fig. 2b), then a sectional partition with a horseshoe-shaped PSD (Fig. 2c), and finally a complete partition with a segmented PSD (Fig. 2d). The latter perforated subtype has an exceptionally high level of AMPAR immunoreactivity [7], which likely translates into an unusually strong synaptic conductance relative to that at other axospinous synapses. A high number of AMPARs at segmented synapses may be necessary for mediating the maximal level of synaptic responses characteristic of certain forms of synaptic plasticity, such as the early LTP phase. The subsequent enduring retention of a relatively lower level of synaptic enhancement during the late LTP phase, and its return to control levels over time, may involve the conversion of segmented, completely partitioned synapses into nonpartitioned perforated subtypes (Fig. 2e–g) and eventually back into non-perforated synaptic junctions (Fig. 2a). The proposed model helps to explain the large degree of morphological heterogeneity among perforated synapses, and indicates a likely association between activity-dependent synaptic restructuring and enhancements in synaptic strength. It has also been postulated that the perforated synaptic subtypes may be intermediates in the process of synapse splitting and division, but there are no data demonstrating the existence of this process.

Pathology

Recent observations indicate that learning and memory disturbances during aging are associated with structural changes in perforated synapses that are likely to have a deleterious effect on their function. It has long been known that aging-related impairments of cognitive functions do not affect all aged individuals: some of them have preserved learning and memory capacities even at advanced chronological age. The reason for such pronounced individual differences in mnemonic functions remains unknown. In a study exploring this problem [10], aged rats were behaviorally tested on a hippocampus-dependent water maze task and separated into groups with impaired or unimpaired spatial learning as compared with young adults. PSD area was estimated in perforated and nonperforated synapses from the stratum radiatum of hippocampal field CA1. The results show that aged learning-impaired rats exhibit a marked (~30%) reduction in perforated PSD area, whereas learning-unimpaired rats do not. This change is highly selective because it does not involve nonperforated PSDs. Given the strong positive correlation between PSD size and AMPAR content among perforated synapses [7], the removal of postsynaptic AMPARs from the PSD may underlie the reduction in PSD area and weaken the efficacy of synaptic transmission. Such a mechanism is also a prime candidate for contributing to the cognitive decline in the subset of aged learning-impaired animals.

References

1. Calverley RKS, Jones DG (1990) Contributions of dendritic spines and perforated synapses to synaptic plasticity. *Brain Res Rev* 15:215–249
2. Geinisman Y (1993) Perforated axospinous synapses with multiple, completely partitioned transmission zones: probably structural intermediates in synaptic plasticity. *Hippocampus* 3:417–434
3. Jones DG, Harris RJ (1995) An analysis of contemporary morphological concepts of synaptic remodeling in the CNS: perforated synapses revisited. *Rev Neurosci* 6:177–219
4. Geinisman Y (2000) Structural modifications associated with hippocampal LTP and behavioral learning. *Cereb Cortex* 10:952–962
5. Nikonenko I, Jourdain P, Alberi S, Toni N, Muller D (2002) Activity-induced changes of spine morphology. *Hippocampus* 12:585–591
6. Ganeshina O, Berry RW, Petralia RS, Nicholson DA, Geinisman Y (2004) Differences in the expression of AMPA and NMDA receptors between axospinous perforated and nonperforated synapses are related to configuration and size of postsynaptic densities. *J Comp Neurol* 468:86–95
7. Ganeshina O, Berry RW, Petralia RS, Nicholson DA, Geinisman Y (2004) Synapses with a segmented, completely partitioned postsynaptic density express more AMPA receptors than other axospinous synaptic junctions. *Neuroscience* 125:615–623
8. Geinisman Y, deToledo-Morrell L, Morrell F, Heller RE, Rossi M, Parshall RF (1993) Structural synaptic correlate of long-term potentiation: formation of axospinous synapses with multiple, completely partitioned transmission zones. *Hippocampus* 3:435–446
9. Toni N, Buchs P-A, Nikonenko I, Povilaitite P, Parisi L, Muller D (2001) Remodeling of synaptic membranes after induction of long-term potentiation. *J Neurosci* 21:6245–6251
10. Nicholson DA, Yoshida R, Berry RW, Gallagher M, Geinisman Y (2004) Reduction in size of perforated postsynaptic densities in hippocampal axospinous synapses and age-related spatial learning impairments. *J Neurosci* 24:7648–7653

Periamygdaloid Cortex

Definition

The periamygdaloid cortex is a paleocortical brain region on the medial surface of the amygdala. It belongs to the uncus of the temporal lobe, and has been described as anatomically heterogeneous.

►Olfactory Pathways

Periaqueductal Gray Matter (PAG)

Definition

The periaqueductal gray matter is the midbrain area surrounding the cerebral aqueduct (of Sylvius) and consisting of different longitudinal columns that initiate stimulus-specific autonomic and antinociceptive responses to external stressors. The lateral column of the periaqueductal gray initiates flight-or-flight sympathoexcitatory responses associated with opioid-independent analgesia. The ventrolateral column elicits hypotension, bradycardia, immobility, and hyporeactivity to the environment, associated with opioid-dependent analgesia.

- Central Regulation of Autonomic Function

Periaxin

Definition

Periaxin is a Schwann cell-specific protein of 147 kDa. It is expressed exclusively by myelinating Schwann cells and is predominately localized to their abaxonal surface. Periaxin is a myelin-related protein that undergoes dynamic changes in its localization during ensheathment and myelination.

- Myelin
- Schwann Cell
- Schwann Cells in Nerve Regeneration

Perifornical Area/Lateral Hypothalamus

Definition

Brain area of the lateral hypothalamus surrounding the fornix, a bundle of fibers that connects the hippocampus with the septal area and tuberomammillary nucleus.

- Hypothalamus
- Hypothalamus, Lateral

Periglomerular Cell in Olfactory Bulb

Definition

Periglomerular cells constitute one type of intrinsic neurons of the olfactory bulb. Their cell bodies are among the smallest in the brain and surround olfactory glomeruli. They usually give rise to a single dendrite that arborizes within a glomerule, and an axon, that extends laterally in the periglomerular region, as far as five glomeruli. Therefore, periglomerular cells participate in both intraglomerular and interglomerular circuits.

Periglomerular cells are not homogeneous, but occur in several distinct subtypes that differ in connectivity, neurochemical content (expressing GABA, dopamine, calbindin, or calretinin, or combinations of these) and electrophysiological properties. Based on connectivity, they are currently classified as type 1 cells, which receive excitatory input from the olfactory nerve, and type 2 cells, which establish few or no synapses with olfactory nerve axons.

Periglomerular cells are one of the few types of neurons that undergo continuous neurogenesis throughout life.

- Dopamine
- GABA
- Olfactory Bulb
- Olfactory Bulb Glomerulus
- Olfactory Nerve

Perilymph

Definition

Fluid similar to cerebrospinal fluid (CSF) inside the bony labyrinth that surrounds the delicate membranous labyrinth. Perilymph has a high sodium content and low potassium content.

- Peripheral Vestibular Apparatus

Perimysium

Definition

The fascia that covers the full perimeter of each muscle fascicle, with the exception of its ends. It forms the wall

of a “tunnel” in which the muscle fascicle operates. It is continuous with the endomysial stroma within the fascicle.

- Intramuscular Myofascial Force Transmission
- Skeletal Muscle Architecture

Period

Definition

1. The time it takes a periodic function to repeat itself once, the time for the completion of a cycle.
2. Name of a clock gene whose mutation alters period length of a circadian cycle, identified originally in the fruit fly, which together with the Cryptochrome proteins suppress transcriptional activation during the dark phase.

- Acoustics
- Clock Genes
- Clock-Controlled Genes

Period (Tau, τ) of Circadian Rhythm

Definition

The time that it takes for the biological oscillator to complete one cycle, to go from start to finish. In the case of circadian oscillators, the period is close to, but not equal to, 24 h. The measurement of period should be made over the course of a number of cycles when the organism is held under conditions of constant dark and fixed temperature. The periods of circadian oscillators are also temperature compensated; that is, the period length does not change in response to alterations in the external temperature. For diurnal organisms, the period is typically longer than 24 h; for nocturnal organisms, however, the period is typically less than 24 h (a finding referred to as Aschoff's rule). The molecular genetic factors responsible for the generation of the circadian period have been the subject of much research.

Although the period length of circadian oscillations is largely determined by these genetic factors, there is also evidence for modest history-dependent regulation of period. The persistence of circadian oscillations under constant conditions and the maintenance of

period in the face of temperature changes are fundamental features of circadian oscillators.

- Circadian Rhythm
- Phase Response Curve (PRC)

Periodic Behavior

Definition

A rhythmic behavior which can be observed to repeat, and is separated by a regular interval of time between adjacent events.

- Peripheral Feedback and Rhythm Generation

Periodic Brain Activation

Definition

Periodic brain activation is associated with the REM state and plays a role in localized recuperative processes and in emotional regulation during sleep.

- Memory and Sleep

Periodic Limb Movements of Sleep

Definition

A sleep related movement disorder consisting of repetitive, involuntary limb movements during sleep.

Electromyographic sensors on the limbs reveal trains of muscle contractions with characteristic shape, amplitude, frequency, and distribution. The limb movements may be temporally associated with arousals from sleep.

The high association with restless leg syndrome and the same targets of therapy suggest that the two disorders share common mechanisms.

- Sleep – Developmental Changes

Periodicity Pitch

Definition

The pitch that is nearly equal to the frequency of a sinusoidal amplitude modulation of a tone or a complex sound.

- ▶ Acoustics
- ▶ Tonotopic Organization (Maps)

Periodontal Ligament

Definition

The collagenous connective tissue that attaches a tooth to the surrounding alveolar bone of the lower (mandibular) or upper (maxillary) jaw.

- ▶ Tactile Sensation in Oral Region

Periodontal Mechanoreceptors

Definition

Receptors that innervate the periodontal ligament and signal information about loads applied to the teeth.

- ▶ Periodontal Ligament
- ▶ Tactile Sensation in Oral Region

Periodontal Pressoreceptors

Definition

Rapidly conducting trigeminal sensory afferent neurons that innervate specialized receptors in the periodontal ligament that anchors the roots of the teeth in the jawbones. They respond to pressure applied to the crowns of the teeth.

- ▶ Mastication
- ▶ Periodontal Ligament

Peri-Personal Space

Definition

- ▶ Visual Space Representation for Reaching

Peripheral Autonomic (Parasympathetic, Sympathetic) Pathway

Definition

Pathway consisting of a population of preganglionic neurons and a population of postganglionic neurons transmitting impulses in the autonomic ganglia and to the effector cells. Each pathway is specified by the target cells it innervates, i.e. as muscle vasoconstrictor, cutaneous vasoconstrictor, sudomotor, cardiomotor etc pathway.

- ▶ Autonomic Reflexes

Peripheral Chemoreception in Respiration

Definition

The major peripheral chemoreceptors are the carotid bodies and the aortic bodies, which convert the hypoxic signals into an increased neural activity to produce reflex responses in the respiratory system. Hypoxic signals from the arterial chemoreceptors are conveyed through the carotid sinus and vagal afferents, which terminate almost exclusively in the nucleus tractus solitarii (NTS) area. The neurons in the NTS project excitatory inputs to the ventral respiratory group (VRG) neurons. Hypoxia initially increases and then slowly decreases ventilation. The initial increase is attributed to stimulation of arterial chemoreceptors and the ensuing slow decline of ventilation is due to the resulting hypocapnia and the central effects of hypoxia.

- ▶ Carotid Body Chemoreceptors and Respiratory Drive
- ▶ Neural Respiratory Control during Acute Hypoxia
- ▶ Nucleus of the Solitary Tract
- ▶ Respiratory Network Responses to Hypoxia

Peripheral Chemoreceptors

► Respiratory Reflexes

Peripheral Clock

► Peripheral Oscillator

Peripheral Feedback and Rhythm Generation

HAROLD J. BELL

Department of Cell Biology and Anatomy, University of Calgary, Calgary, AB, Canada

Synonyms

Sensory modulation of central pattern generators; CPGs; Afferent input to rhythm generating networks

Definition

Rhythmic motor behaviors such as walking, wing beating, chewing and breathing are all governed by networks of one or more neurons, named central pattern generators (CPGs). By definition, the CPG is able to generate and maintain a basic patterned neuronal activity that is absolutely fundamental to producing the behavior which it governs. However, an animal's behavior must take into account conditions or changes in the environment such that the behavior remains relevant and appropriate. Behavior is kept relevant and appropriate by integrating sensory feedback into the rhythm generation process. Sensory feedback is a general term which refers to neural signals transduced through a wide variety of sensory modalities (chemoreception, mechanoreception (► [Mechanoreceptor](#)), etc.). Peripheral feedback specifically refers to sensory feedback that is transduced outside of the central nervous system, and provides the CPG network with neural signals encoding information relevant to behavior. Thus, peripheral feedback is intimately related to and is an important component of the process of rhythm generation.

Characteristics

Rhythm Generation and Behavior

Repetitive motor acts are involved in a seemingly endless number of behaviors across animal species: walking, crawling, flying, swimming, feeding and breathing are all excellent examples. Because of the complex and repetitive nature of the motor acts involved in coordinating these behaviors, networks of neurons have evolved that are extremely efficient at generating the basic timing and pattern of motor neuron discharge that underlie them, in a highly reproducible fashion. These networks of neurons are almost exclusively located in ganglia or the nuclei of brains within intricate central nervous systems, and therefore are commonly called central pattern generators (CPGs).

By definition, a CPG network is capable of spontaneously generating a rhythmic activity that is sufficient for eliciting the motor behavior that it governs, even in the absence of other synaptic inputs.

CPGs have been studied in considerable depth for a number of behaviors observed across numerous species [1]. Given the diversity of behaviors and therefore the CPGs that govern them, it is difficult to suggest that any one specific behavior or CPG is typical of all others. Nevertheless, this diversity also means it is advantageous to focus upon a specific behavior in order to discuss how CPGs can be modulated by peripheral feedback. For this reason we shall focus our discussion upon breathing behavior, and the respiratory rhythm generator that drives this behavior.

Respiratory Rhythm

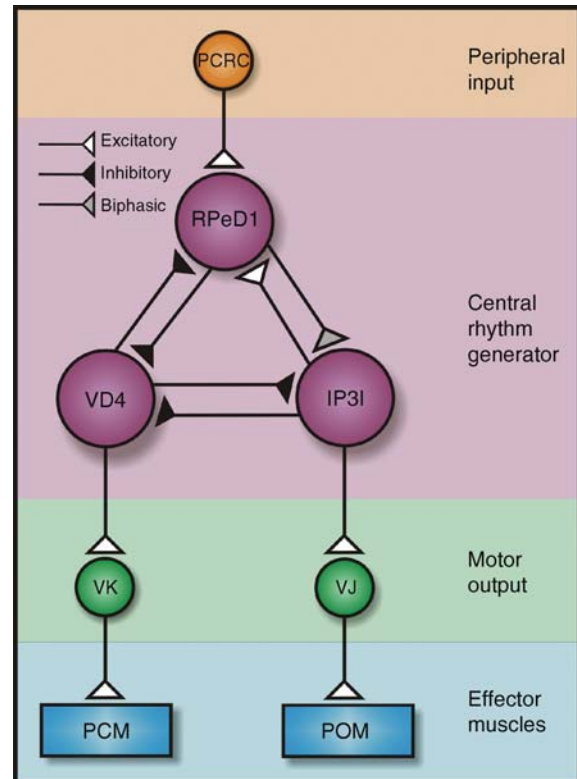
Breathing is perhaps the quintessential example of a rhythmic behavior, as it is essential to the survival of countless animal species from insects, to fish, to mammals. Breathing is a homeostatic motor behavior, which allows the animal to obtain oxygen from, and eliminate carbon dioxide into the external environment. Across *Animalia* many breathing patterns, from regular periodic rhythms (► [Periodic behavior](#)), to episodic patterns (► [Episodic behavior](#)) can be found, and even within some species these patterns are labile. As a motor behavior, breathing requires the coordinated activation of respiratory pump muscles. The CPGs controlling breathing in most animals are very complicated, and so in most cases very little is known about the detailed synaptic connectivity and neurons involved in respiratory rhythm generation. Indeed, if one considers the extent of behaviors and therefore related CPGs present in the animal kingdom, relatively few examples are available of fully described networks.

Invertebrate model systems have been fundamental in advancing our understanding of nearly every aspect of modern neuroscience, and in no field has this been more so than in the study of central rhythm generation.

Presently, fully described CPG networks are limited to those identified in invertebrate species. This is because the central neurons of invertebrates exist within ganglia, and many are readily identifiable based upon location and morphology, making it possible to study an individual cell involved in a particular behavior across multiple animals of the same species. Therefore invertebrates are especially amenable to the study of rhythm generation since networks can be mapped from identified cells. One model system wherein the essential central neuronal components of the respiratory CPG have been identified is the pulmonate freshwater mollusk *Lymnaea stagnalis* [2]. *Lymnaea* are aquatic air breathers, and their breathing is a hypoxia-dependent behavior. *Lymnaea* breathe through coordinated motor output to the muscles of the mantle cavity and pneumostome. Contraction of muscles in the mantle cavity and pneumostome opening muscles allow stale air to be expelled from and fresh air to subsequently be drawn into the animal's rudimentary lung. The core of the CPG controlling this behavior consists of three identified cells which have been studied both *in vivo* and *in vitro* (see Fig. 1).

By contrast, in mammals the respiratory central pattern generator is comparatively complex, and for good reason; respiratory control also needs to accommodate other related behaviors aside from breathing such as feeding, sniffing, licking, and vocalization. Not surprisingly, the intricacy of the mammalian central nervous system has made it rather difficult to characterize the respiratory CPG. Impressive progress has been made however, and central respiratory-related neuronal populations are known to be distributed bilaterally throughout a number of nuclei in the medulla and pons (see Fig. 2). Species differences aside, the mammalian CPG controlling breathing behavior is the topic of great controversy and active research [3]. Regardless of this complexity, breathing remains a motor behavior involving the rhythmic activation of respiratory pump muscles enabling lung ventilation.

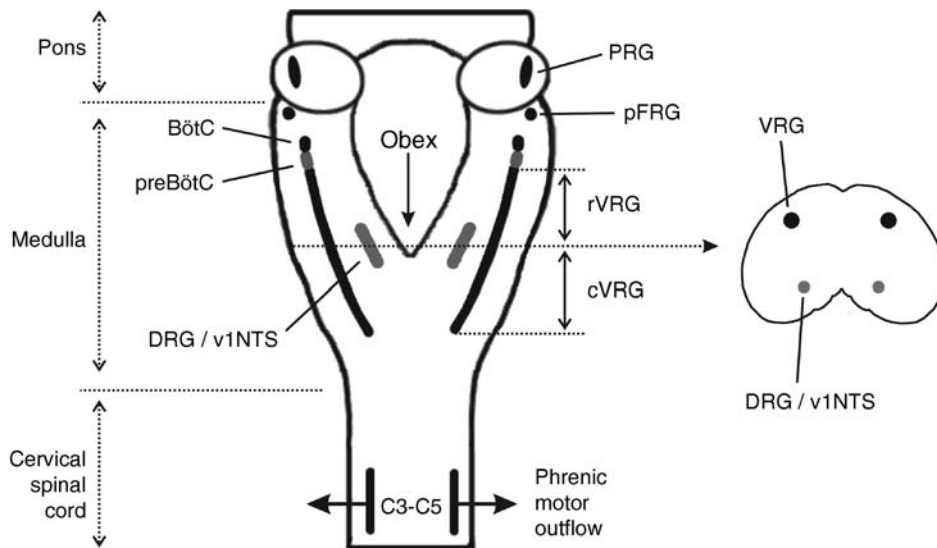
Inspiratory muscles, mainly the diaphragm and external intercostal muscles, act to increase thoracic volume and draw atmospheric air into the lungs. Expiration is normally a passive process of elastic recoil during resting breathing, however expiratory muscles are required for forceful expiration at higher levels of ventilation, and these muscles are mainly the abdominal muscles and the internal intercostal muscles. During resting breathing, the most important respiratory muscle by far is the diaphragm, which contracts during inspiration and is controlled by motor innervation via the phrenic nerve. Characterization of respiratory neurons in the medulla has therefore been accomplished by describing their activity in relation to phrenic nerve activity. If the rhythmic activity of a central neuron has the same period as phrenic activity, then the cell can be designated a respiratory neuron. Further characterization takes into



Peripheral Feedback and Rhythm Generation.

Figure 1 A schematic representation of the only fully described respiratory CPG; that identified in the pulmonate freshwater snail, *Lymnaea stagnalis*. This respiratory CPG is composed of three interneurons, which have been identified and named as follows: right pedal dorsal 1 (RPeD1), visceral dorsal 4 (VD4), and the “input 3” interneuron IP3I. The opening and closing of the respiratory orifice, the pneumostome, is accomplished through patterned activity of motor neurons controlling pneumostome opening muscles (POM) and pneumostome closing muscles (PCM). Note that the central rhythm generating neuron RPeD1 receives an excitatory chemical synaptic input from oxygen-sensitive peripheral [chemoreceptor](#) cells (PCRCs) located in the periphery, which act to initiate and subsequently regulate the activity of this rhythm generation network. As such, peripheral inputs to the CPG are an important component of the rhythm generation process.

account the phase relationship between the cell and phrenic activity (see Fig. 3). For example a respiratory neuron that fires bursts of action potentials in sync with phrenic activity is called an inspiratory neuron. Conversely, a cell that fires during phrenic quiescence, it is called an expiratory neuron. More specific classification takes into account more specific phases of the respiratory cycle (e.g. pre-inspiratory, late expiratory), and the pattern of discharge of the neuron during its period of activity (e.g. augmenting, decrementing, or constant), and



Peripheral Feedback and Rhythm Generation. Figure 2 A schematic representation of those brainstem regions known to contain respiratory neurons in mammals, along with their approximate anatomical locations. Shown is a schematic view of the brainstem from the dorsal coronal perspective, with a transverse section at the level of the obex. In contrast to the respiratory CPG of *Lymnaea* (shown in Fig. 1), the rhythmic motor output to respiratory muscles in mammals is generated by a complex network of many neurons bi-laterally distributed throughout several regions of the pons and medulla. Relevant neuronal populations are represented as follows: PRG, pontine respiratory group; pFRG, parafacial respiratory group; BötC, Bötzing complex; preBötC, pre Bötzing complex; DRG, dorsal respiratory group; cVRG, caudal ventral respiratory group; rVRG, rostral ventral respiratory group; v1NTS, ventrolateral nucleus tractus solitarii.

these characteristics are used to functionally differentiate respiratory neurons from one another [4].

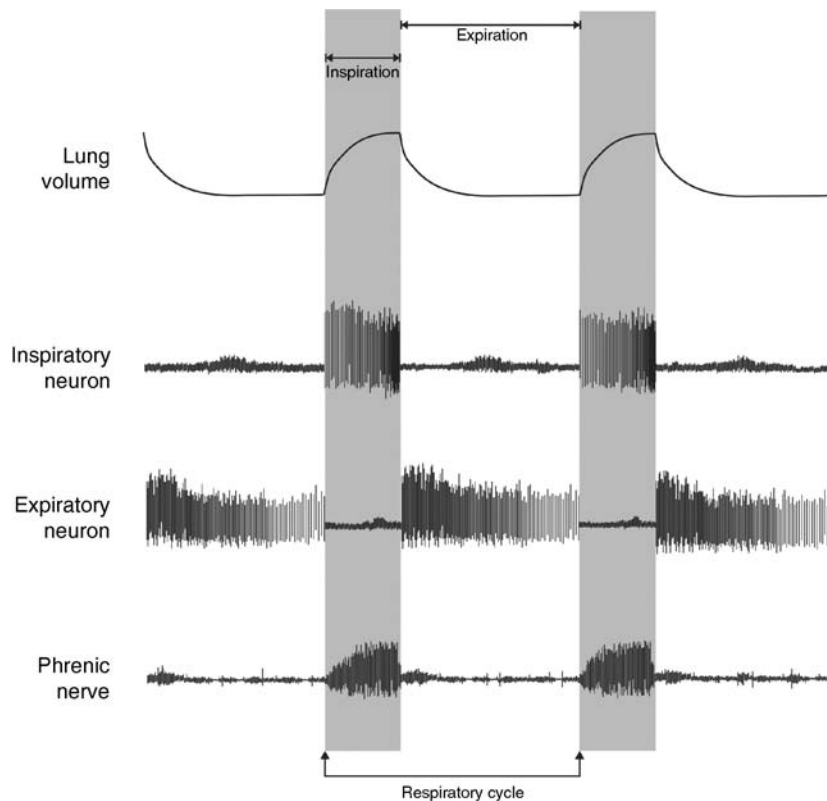
Of the populations of neurons in the medulla that have been classified as respiratory neurons, it has long been debated as to which of these were actually involved in generating the base rhythm, and could therefore be designated, “the CPG.” Two groups of neurons in the brainstem have been identified that are presently believed to be essential to the generation of a basic respiratory rhythm: (i) A region of the ventrolateral medulla named the preBötzinger complex (PreBÖT), and (ii) a region of the medulla ventrolateral to the facial nucleus near the ventral surface, named the parafacial respiratory group (pFRG). While the precise role of these two neuronal populations in respiratory rhythm generation remains the focus of much ongoing research, it has recently been proposed they may form a coupled network oscillator, with the former responsible for generating inspiration, and the latter generating active expiration phases of the respiratory cycle.

The Role of Peripheral Feedback in Respiratory Rhythm

It has been widely accepted since the early 1960s that while a CPG can independently function to generate a basic rhythmic motor behavior, sensory feedback from the periphery is necessary for modulating the timing and amplitude of events so that this behavior remains relevant to the environmental demands on the animal

[5]. In this regard, the respiratory CPG is certainly no different, and several forms of afferent information provide a potent modulating influence over rhythmic output. Input from airway receptors can elicit cough or sneeze airway defense mechanisms. Inputs from **carotid body chemoreceptors** provide a potent drive to ventilation when arterial blood becomes hypoxic, hypercapnic, or acidic. Group III and IV afferents in the skeletal muscle are able to stimulate breathing, and are believed to be important in coupling the cardiovascular and respiratory systems to regulate gas exchange. Stretch receptors in the lungs are important in shaping the respiratory cycle and timing the inspiratory and expiratory phases of the breathing cycle. Cutaneous thermoreceptors can elicit a powerful gasp reflex which has been documented during sudden cold water immersion. In aquatic air breathing mollusk *Lymnaea stagnalis*, mechanosensory input to the respiratory CPG is required to gate the episodic breathing rhythm so that the respiratory orifice only opens at the water surface, and a similar mechanism is likely to exist in other aquatic air breathers.

Clearly there are many different modalities of peripheral **sensory input** which modulate the respiratory CPG, but there are also a range of influences that sensory input can have on the characteristics of the respiratory rhythm. Some inputs typically affect rhythm only very briefly over one respiratory cycle (i.e. cough or sneeze reflexes), while some involve



Peripheral Feedback and Rhythm Generation. Figure 3 Phase relationships between rhythmic breathing behavior, phrenic nerve activity, and inspiratory and expiratory respiratory neurons in the mammalian brainstem. A neuron which fires during the interval of phrenic activity can be described as an inspiratory neuron, since this neuron is active during the inspiratory phase of rhythmic breathing behavior (i.e. when lung volume is increasing). Conversely, a neuron which selectively fires during phrenic quiescence can be designated a expiratory neuron since it is active during the expiratory phase of rhythmic breathing behavior (i.e. when lung volume decreases). Further characterization takes into account the firing pattern of the respiratory neuron during its period of activity (e.g. augmenting, decrementing or constant firing frequency), and the specific phase of the inspiratory or expiratory cycle in which it is active (e.g. early or late).

shaping the rhythm during each breath cycle (i.e. lung stretch receptors) and others affect the entire respiratory cycle over the course of many breaths (carotid body chemoreceptors).

Mechanisms of Peripheral Modulation of Respiratory Rhythm

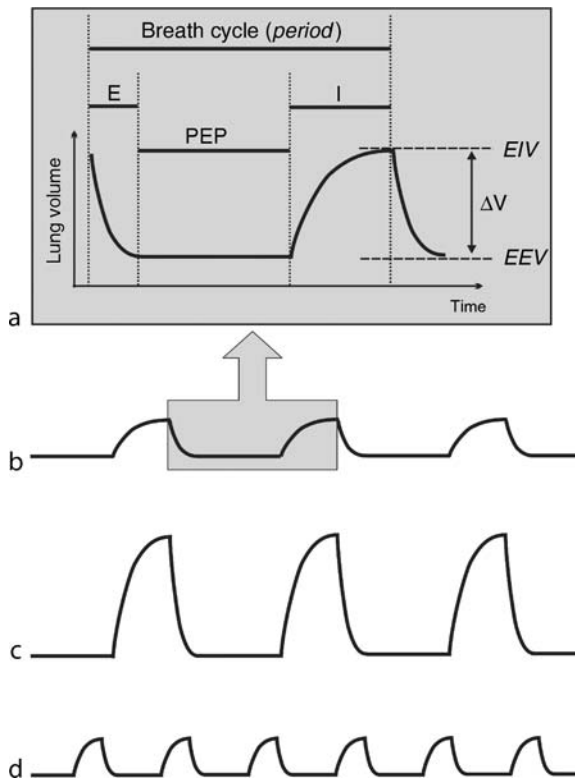
As we have seen, peripheral feedback is involved in modulating respiratory rhythm such that breathing can be matched to the needs of the organism. Whether this is a sustained respiratory drive as occurs during exercise, or a transient effect as occurs during protective airway reflexes, the respiratory rhythm is open to modulation from afferent input.

The main characteristics of respiratory rhythm that can be modulated are breathing frequency, or the number or breathing cycles per unit time, and the amplitude of the motor act, or breath size. These features of the breath cycle are shown in more detail in Fig. 4. Since the pathways and putative mechanisms of modulation of

breathing rhythm depend greatly upon the input signal, we will examine one select example at greater depth.

Carotid Body Chemoreceptor Inputs

The mammalian carotid body chemoreceptors are arterial chemosensory organs that increase breathing in conditions of [hypoxia](#), hypercapnia, or acidosis. Increased chemoreceptor stimulation causes an increase in afferent output that can be measured in the carotid sinus nerve which innervates the organ. Carotid body afferent inputs to the brainstem are first conducted via neurons located mainly within the petrosal ganglion, subsequently via afferent fibers in the glossopharyngeal (IXth cranial) nerve. The [carotid body chemoreceptor inputs](#) ([Chemosensory input](#)) affect respiratory rhythm as follows: Afferent input resulting from either carotid body stimulation or direct stimulation of the carotid sinus nerve elicits a decrease in inspiratory duration leading to an increase in breathing frequency, and an increase in the amplitude of integrated phrenic



Peripheral Feedback and Rhythm Generation.

Figure 4 A diagrammatic representation of those aspects of the breathing cycle which are dictated by final output of the respiratory rhythm generator. (a) an expanded view of one cycle of rhythmic breathing behavior, as shown in (b). The change in lung volume during the breath cycle (ΔV) can be altered by changing the end-inspiratory volume (EIV) or the end-expiratory volume (EEV). In addition, the durations of inspiration (I), expiration (E), and the post-expiratory pause (PEP) can be altered so as to change the period of the breath cycle. Lung ventilation can be increased by augmenting ΔV (as shown in (c)) or by decreasing the period of the breath cycle (as shown in (d)), or any combination of the two. Peripheral inputs modulate respiratory rhythm and therefore aspects of the breath cycle, as shown in (a), such that rhythmic breathing behavior remains relevant to the needs of the animal.

whole nerve activity. Simply stated, carotid input to the respiratory CPG leads to an increase in ventilation through increasing breathing rate and breath size.

The central respiratory pathways involved in this response have been studied in some further detail. Within the brainstem, most of the sensory afferents from the carotid sinus nerve show arborizations within the nucleus of the solitary tract, or nucleus tractus solitarius (NTS), specifically an area of the commissural subnucleus of the NTS including what has been named the dorsal respiratory group (DRG) [6]. The synaptic connectivity and therefore the mechanisms of influence of carotid

sensory afferents are not well described beyond this level of the medullary respiratory network. However, carotid sensory afferents are known to release glutamate in the NTS which is believed to be primarily responsible for the increase in breathing via its action on NMDA receptors at this site. The involvement of multiple neurotransmitters and neuromodulators is likely, though specific details remain a topic of ongoing study.

The overt effects of activation of carotid afferents terminating in the NTS upon rhythm generation have been further documented at the level of respiratory neuronal populations in the medulla including those neurons of the Pre-Böt complex believed to be an important component of the respiratory CPG. Unilateral activation of carotid afferents terminating in the NTS elicits bi-lateral changes in the rhythmic activity of inspiratory driver neurons in the rostroventrolateral medulla; these inspiratory neurons are inhibited and therefore their firing duration is decreased. Afferent stimulation also has the effect of concurrently exciting pre-motor inspiratory neurons in the caudal ventral respiratory group and in the DRG, increasing the drive to phrenic motoneurons [7].

Kinetics of Neuromodulation of Respiratory Rhythm

The activation of carotid afferents is able to elicit changes in respiratory rhythm, which take only a couple of respiratory cycles to achieve their maximal effect ($\tau \sim 10$ s in cats). The removal of carotid input results in a return to baseline rhythmic activity that has a slightly longer time course ($\tau \sim 45$ s, again in cats). This apparent “inertia” in the respiratory rhythm generator, which has been called “short term potentiation” (STP) [8] has been well documented, yet the mechanisms involved are not well understood. Slower onset, longer-lasting alterations in respiratory rhythm have also been documented, that can persist long after the input stimulus has returned to baseline levels. This phenomenon, called long term facilitation (LTF), results in augmented respiratory rhythm lasting for more than one hour after removal of peripheral input to the CPG. One particular stimulus that is capable of eliciting LTF is **intermittent hypoxia**, as sensed by the carotid body chemoreceptors. After repeated hypoxic episodes (for example 3×5 min episodes, separated by 5 min of normoxia), both the frequency and amplitude of phrenic nerve discharge has been documented to remain augmented for hours post-stimulus [9]. This phenomenon has now been documented to various extents in multiple animals in different degrees of reduction, including rats, cats and rabbits. While the phenomenon has proven less robust in some cases than others, LTF in respiratory rhythm is nevertheless a fascinating example of how afferent input can modulate rhythm generation via a CPG, even long after the afferent signal has been removed.

Summary

As we have seen, breathing is an excellent example of a rhythmic behavior that is governed by a central network of neurons. This network in mammals resides in the ponto-medullary brainstem, and receives peripheral inputs from many modalities that are capable of modulating the depth and rate of breathing. While the pathways and mechanisms by which the respiratory CPG is influenced by sensory afferents are specific to this system, it nevertheless illustrates the importance of peripheral feedback in the process of rhythm generation. This is a general neurophysiological principle that applies equally to most rhythmic behaviors across *Animalia*: afferent feedback is essential for ensuring that rhythm generation via CPG networks remains appropriate to the environmental demands on the organism.

References

1. Marder E, Calabrese RL (1996) Principles of rhythmic motor pattern generation. *Physiol Rev* 76(3):687–717
2. Syed NI, Bulloch AG, Lukowiak K (1990) In vitro reconstruction of the respiratory central pattern generator of the mollusk *Lymnaea*. *Science* 250(4978):282–285
3. Onimaru H, Homma I (2006) Point:Counterpoint: the parafacial respiratory group (pFRG)/pre-Botzinger complex (preBotC) is the primary site of respiratory rhythm generation in the mammal. *J Appl Physiol* 100(6):2094–2095
4. Duffin J, Ezure K, Lipski J (1995) Breathing rhythm generation: focus on the rostral ventrolateral medulla. *News Physiol Sci* 10:133–140
5. Wilson D (1961) The central nervous control of locust flight. *J Exp Biol* 38:471–490
6. Finley JC, Katz DM (1992) The central organization of carotid body afferent projections to the brainstem of the rat. *Brain Res* 572(1–2):108–116
7. Morris KF, Arata A, Shannon R, Lindsey BG (1996) Inspiratory drive and phase duration during carotid chemoreceptor stimulation in the cat: medullary neurone correlations. *J Physiol* 491(Pt 1):241–259
8. Wagner PG, Eldridge FL (1991) Development of short-term potentiation of respiration. *Respir Physiol* 83(1):129–139
9. Bach KB, Mitchell GS (1996) Hypoxia-induced long-term facilitation of respiratory activity is serotonin dependent. *Respir Physiol* 104(2–3):251–260

Peripheral Glial Cell

Definition

Glial cells wrapping peripheral neurons in *Drosophila*.

- [Alternative Splicing and Glial Maturation](#)
- [Glia Cells](#)

Peripheral Nerve Regeneration and Nerve Repair

RAJIV MIDHA

Division of Neurosurgery, Department of Clinical Neurosciences, University of Calgary, AB, Canada

Synonyms

Axonal regeneration

Definition

► [Nerve regeneration](#) is the process of axonal regrowth within peripheral nerve following injury. Basic science and clinical studies underscore both the possibilities and failure of spontaneous axonal regeneration after peripheral nerve injuries. Historical and current methods of nerve repair at the tissue level take advantage of the natural tendency of peripheral axons to grow when provided with a suitable (micro)environment. New and emerging nerve repair strategies, building on key discoveries at the cellular and molecular, have the potential to further significantly improve the outcome from the repair of nerve injuries.

Characteristics

Nerve Regeneration Outcomes and Challenges

Peripheral nerves have the potential to regenerate axons and reinnervate end-organs, with resulting good functional recovery. Indeed, this is the case with all minor nerve injuries, such as neuropraxia, where the axon remains intact, and most purely axotmetic injuries, where axons are interrupted but the degree of internal damage is minimal. In the latter circumstance, regenerating axons use their existing ► [endoneurial pathways](#) to specifically reinnervate their own precise target end-organs, as confirmed in recent experiments using bioengineered fluorescent mice [1].

Outcome following more severe peripheral nerve injury (PNI) however remains variable and often very poor. At least three important factors contribute to the relatively poor outcome. The first challenge is the pathology at the tissue level. The majority of clinical PNI exhibit both a loss of axon continuity and a significant disruption in the internal connective tissue structures. The resulting scarring within the nerve or a frank gap (with lacerating injuries) presents a formidable barrier to regenerating axons, preventing them from effectively innervating the distal nerve stump. These are currently managed with a repair of the divided nerve or, for the usual scenario of longer gaps or scar segments that need to be resected, placement of interposed nerve grafts. Direct nerve or nerve graft repair unfortunately do not obviate the misdirection of axons. This

introduces the second biological challenge, which is at the cellular level. Even with the most meticulous repair, the endoneurial tubes can never be reapproximated exactly and this results in mismatching of regenerating axons at the site of suture, or within the graft, leading to inappropriate (non-specific) reinnervation and subsequent poor recovery in function. The third challenge may be considered as a quantitative one, which is associated with chronic denervation (**►Chronic nerve denervation**) of the distal nerve. Chronic denervation is common because of the often extensive injury zone that prevents any axonal outgrowth or (even if outgrowth occurs) the relatively slow rate of regeneration. As a consequence, the distal nerve segment remains chronically devoid of regrowing axons. The resulting prolonged denervation of Schwann cells (SCs) appears to be a critical factor which makes them unreceptive for axonal regeneration, and is the single most important quantitative contributor to poor end-organ reinnervation [2].

Spontaneous Axonal Regeneration After Nerve Injuries

The details of the basic processes involved in nerve degeneration and early regeneration are outlined in detail elsewhere in this Encyclopedic Series (see the contribution by Doug Zochodne). Herein, I will summarize some key concepts, with a more detailed focus on the critical role played by the denervated nerve, distal to the nerve injury.

The injury to an axon is associated with a plethora of changes in the neuronal cell body that shift its phenotype from a neuron involved in maintenance/neurotransmission, to a regenerating one, with a corresponding up-regulation of **►regeneration associated genes (RAGs)**. Regeneration from neurons requires severed axons to redeem their original axoplasmic volume by extending their processes distally. New axons sprout from one or two internodes proximal to an injury zone. These spontaneously sprouting daughter axons, supported by SCs, and surrounded by a common basal lamina tube are termed a “regenerating unit.” Therefore in regeneration, the number of neurons does not increase, but rather surviving neurons regenerate their cellular processes in concert with their surrounding microenvironment. Key components of the microenvironment involve a very close and intimate relationship between regrowing axons, and the supporting glial SCs, which must both proliferate and migrate [3]. Indeed, the initial stages of axonal regeneration are highly dependent on SCs which lead the regrowing axons across the nerve injury site.

Severance of a peripheral nerve results in **►Wallerian degeneration** in all axons distal to the injury site, evidenced by the disintegration of axoplasmic microtubules and neurofilaments. The majority of axons along the distal stumps of transected nerves are reduced

to granular and amorphous debris within 24 h; by 48 h, the myelin sheath has begun to transform into short segments that then form into ovoids. Activated macrophages invade the degenerating distal nerve stump and phagocytose the disintegrating nerve fibers and myelin. There is an accompanying proliferation of the acutely denervated SCs, which now alter their gene expression, and change phenotypically from myelinating to growth supportive [4].

As axons from the proximal nerve stump arrive in the nerve distal to original injury, SCs and basal lamina tubes are reinnervated and thereby supported, which in turn, provides an excellent trophic and cell-adhesive environment for further axonal regeneration [5]. Regenerating axons, when contacting SCs, release neuregulins from their growth cones which bind to erbB receptors on the SCs to mediate a second phase of SC proliferation. SCs secrete chemoattractive factors, including cytokines such as interleukin-1 β , leukemia inhibitory factor and monocyte chemoattractant protein-1, that recruit macrophages into the denervated nerve stumps [5]. Cytokines, derived from both the SCs as well as the macrophages that enter the nerve, drive the expression of the non-myelinating, dedifferentiated “denervated” phenotype of the SCs which proliferate, form the **►bands of Bungner** (SC lined basal lamina tubes) and guide regenerating axons within the distal nerve stump [4]. The switch in SC phenotype is associated with up-regulation of several growth associated genes including several neurotrophic factors, p75 NTR, glial fibrillary acidic protein, GAP-43, netrin-1 and the transcription factor, Krox-24, which all support axonal regeneration [5]. In summary, the capacity of the denervated distal nerve to support axonal regeneration depends on proliferating acutely denervated SCs within the basal lamina tube which are essential for guiding regenerating axons to the end-organs.

Repairing Nerve Injury Gaps: Nerve Grafts, Electrical Stimulation and Nerve Conduits

The majority of clinical PNI leave the nerve grossly intact, but nevertheless exhibit loss of axon continuity and a severe disruption in the internal connective tissue structures. Scarring within the nerve presents a barrier to regenerating axons. Nerve repair requires resection of the scarred segment and repair of the resulting lengthy nerve gap, usually with a nerve graft, typically procured from another area of the patient’s own body (nerve autograft). The nerve graft contains surviving SCs and basal lamina endoneurial tubes, which provide neurotrophic support, as well as favorable cell and endoneurial tube surface adhesion molecules to regenerating axons [5]. Nerve grafts therefore provide a seemingly optimal tissue bridge that regenerating axons from the proximal nerve stump exploit to innervate the distal stump. With the advent of the operating microscope and microsurgical techniques, Millesi improved clinical results and

popularized the use of nerve autografts. The outcomes, associated with using nerve grafts, are best for nerves which are primarily innervating one or a few discrete motor or sensory targets, and especially where the repair is close to the target end-organ. For the more proximal injuries, ones requiring lengthy grafts and ones involving nerve elements which innervate a variety of motor and sensory targets, the outcomes remain poor. Moreover, results of microsurgical repair, which is essentially at the tissue level, have reached a plateau over the last few decades.

A major shortcoming with the nerve graft technique is the biological constraint, which cannot be overcome by further progress in microsurgical techniques. Even with the most meticulous repair, regenerating axons at the site of suture, or within the graft, get misdirected or lost, leading to inappropriate (non-specific) and incomplete reinnervation, respectively. Innovative recent investigations with nanoscale engineered devices suggest that some day surgery at the cellular level to splice and repair individual axons may be feasible. Recent insights into the nuances of axonal regeneration however provide potential for some new therapies that are even readily accessible soon. We now understand that axonal outgrowth is not synchronous, but rather staggered, so that some pioneering axons grow out early, while others lag far behind. In fact, many of the lagging axons get delayed at suture repair sites, which in the case of a nerve graft are compounded, involving two separate repair locations. Emerging evidence also suggests that pioneering motor axons, for example, may prefer to associate with corresponding “motor” SCs, based on their surface-specific basement membrane molecules. These pioneering axons may start the process, and they together with their migrating SCs facilitate similar axons to follow by offering these cues as required. Studies by Brushart and colleagues show that motor axons particularly may be biased in their selection of distal targets, preferring phenotypically appropriate rather than inappropriate endoneurial pathways in the distal nerve, so that ultimately some ►**preferential motor reinnervation (PMR)** is exhibited [6]. Exciting recent work by Gordon and Brushart suggests that epochs of electrical stimulation as short as one hour have a significant influence not only on synchronizing the initial re-growth of motor axons, but also on possibly enhancing PMR. Clinical trials to assess the utility of short duration electrical stimulation on improving the outcome of nerve repair are therefore warranted.

In an attempt to provide a more suitable environment for regenerating axons to sample and respond to appropriate *endogenous* directional cues, many investigators have proposed using an artificial (non-nerve) conduit interposed between the proximal and distal nerve stumps. Moreover, a bioengineered graft may allow the introduction of *exogenous* therapies that build

on our rapidly expanding knowledge of axonal guidance. Axons are guided to their targets by growth cones, specialized structures at the tip of axons, that respond to the coordinated action of many contact-mediated cues provided directly or indirectly by SCs and diffusible cues, which are either attractive or repulsive. A short list of candidate molecules to consider include the classical neurotrophins, neurotrophic cytokines (including CNTF, IL-6, oncostatin, and LIF), other neurotrophic factors (including insulin, IGF-1 and GDNF), cell adhesion molecules (including NCAM, L1 and N-cadherin), and extracellular matrix proteins (including laminin, tenascin C, fibronectin and heparan sulfate proteoglycan) [5]. By exogenously providing the most appropriate or suitable cues, we may be able to profoundly influence axonal regeneration within the nerve conduit. The clinical utility of such a strategy is apparent when considering the example of repair of nerves to the hand, where the median nerve is paramount for sensation whereas the ulnar nerve is critical for discrete motor function of the digits. In these instances, the conduit repair can be endowed with specific growth factors or other molecules that will bias the regeneration towards a population of axons (motor vs. sensory) to achieve improved specificity of reinnervation. Artificial nerve conduits or tubes are already proven and in clinical use for short injury gaps of 3 cm or less in humans. Advances in bioengineering, coupled with our understanding of how to effectively deliver growth factors, cell adhesion molecules and other therapies within the artificial nerve graft, should lead to major advances in improving both the quantity and specificity of axonal regeneration through the nerve conduit [7].

Deleterious Changes Associated with Chronic Nerve Denervation

So far, the therapies considered in this essay have focused on the repair of the nerve injury site or nerve injury gap. We now turn our attention to the critical distal nerve environment. Denervated SCs initially up-regulate neural cell adhesion molecule and basement membrane components (including laminin), which are used for attachment and growth of the regenerating axons. A growth supportive environment of the distal nerve is unfortunately not maintained unless axonal contact is re-established. Progressive regression of the capacity of the denervated SCs to sustain their growth permissive phenotype [8] and the progressive decline in numbers of SCs in the chronically denervated distal nerve stumps underlie the loss of capacity to support axonal regeneration [9]. Deleterious changes that affect axonal growth become increasingly pronounced over time, and are coupled with a progressive decline in the number of reinnervated motor units after chronic denervation [2]. In recent experiments, we have demonstrated that immediate innervation of the distal nerve, as

compared to chronic denervation, greatly improves subsequent re-innervation, confirming that the failure in regeneration is related to the profound changes in the distal stump from chronic denervation. A critical component of this unreceptive environment in the distal nerve is the chronically denervated SC whose growth support properties appears to be “turned off” [5].

The above biological issue is very clinically relevant as delayed nerve repairs occur frequently in clinical practice. The reason this occurs is because the majority of nerve injuries leave the nerve in physical continuity with an often unknown propensity to spontaneously recover, a process which unfolds over several weeks to months. Hence, most patients undergo appropriate surgical exploration several months after injury and receive a delayed nerve repair. Even patients who have immediate nerve repair are subject to distal nerve denervation for considerable periods as the rate of regeneration is relatively slow (~ 1 mm/day in humans), and, given that nerve injuries are far from their end-organs, the distances that regenerating nerve fiber need to grow very long. Hence, almost all severe human nerve injuries creates a situation in which the SCs of the distal nerve are chronically denervated [5].

Therapies to Counteract Chronic Distal Nerve Denervation

Fortunately, the clinical paradigm of ► **nerve transfers** has emerged a powerful means of bypassing the long zone of chronically denervated nerve. Nerve transfers essentially involve the repair of a distal denervated nerve element using a proximal foreign nerve as the donor of neurons and their axons which will reinnervate the distal targets. The concept initially arose to sacrifice the function of a donor (lesser valued) nerve/muscle to revive function in the recipient nerve and muscle that will undergo reinnervation. Nerve transfers have become increasingly utilized for the repair of brachial plexus injuries, especially where the proximal motor source of the denervated element is absent because of avulsion from the spinal cord. Increasingly advocated are the use of transfers in situations where the proximal motor source is available, but the regeneration distance is so long that the outcome would be poor. A nerve transfer into the denervated distal nerve stump, but deliberately chosen so as to be very close to the motor end-organ, would then restore greater function as compared to a very proximal nerve graft repair.

Biological means of protecting the distal denervated nerve are emerging. One strategy is the exogenous use of cytokines (such as TGF- β), normally produced during Wallerian degeneration, to counteract the deleterious effects of chronic denervation and to maintain the growth-promoting denervated SC. In a recent experiment, chronically denervated SCs, exposed to TGF- β and forskolin, when infused into a nerve regeneration

chamber, dramatically increased the number, size and myelination of regenerating axons, as compared to SCs without pre-treatment. Other research laboratories are exploring gene therapy approaches, using lentiviruses or other vectors to augment or resurrect the repertoire of regeneration associated molecules expressed by the denervated SC.

Since chronically denervated SCs appear to become effete, another logical approach is to support the distal denervated nerve environment by replacing lost cells with those derived exogenously. SC infusion has been successful in promoting regeneration and remyelination of the injured peripheral nerve. However, human SCs must be derived from invasive nerve biopsies and have a limited, lengthy expansion *in vitro*. It is thus desirable to identify a more accessible source of SCs for transplant therapies. Bone marrow stromal cells, adipose tissue derived stem cells and skin derived precursor stem cells have all been shown to generate functional SCs that can be used for transplantation in nerves [10]. When stem cells derived from skin were transplanted into artificial nerve guidance tubes bridging a 16-mm gap in rodent sciatic nerve, there was promising improvement in behavioral, electrophysiological, and morphometric parameters measured over vehicle control. It is therefore conceivable that skin derived SCs may be very useful in models of chronic nerve injury, either by infusing them into a chronically denervated distal nerve or perhaps immediately after injury as a protective treatment in an attempt to avoid distal changes associated with chronic injury. If experimental studies prove benefit, we anticipate that nerve repair in the future in patients will be augmented by the use of their own (autologous and cultured) skin-derived SCs, easily procured, via relatively non-invasive skin graft harvesting.

Conclusion

Our basic understanding of nerve and axonal regeneration has increased tremendously over the last century, with corresponding gains in our ability to repair clinical nerve injuries. We can already overcome the challenge associated with lacerating nerve injuries and severe nerve injuries in continuity with precise repairs at a tissue level using microsurgical techniques, nerve grafts and short length artificial nerve conduits. We are on the verge of the next (cellular) generation of nerve repair using modalities such as specific molecular therapy, electrical stimulation, and bioengineered and micro fabricated devices. These approaches promise to allow improved synchronization of axonal regeneration and more exact specificity of reinnervation. While distal targeted nerve transfers have already had a clinical impact, in the near future gene and (stem) cell therapy approaches to augment and resurrect the distal denervated nerve environment are anticipated.

References

1. Nguyen QT, Sanes JR, Lichtman JW (2002) Pre-existing pathways promote precise projection patterns. *Nat Neurosci* 5:861–867
2. Fu SY, Gordon T (1995) Contributing factors to poor functional recovery after delayed nerve repair: prolonged denervation. *J Neurosci* 15:3886–3895
3. Chen YY, McDonald D, Cheng C, Magnowski B, Durand J, Zochodne DW (2005) Axon and Schwann cell partnership during nerve regrowth. *J Neuropathol Exp Neurol* 64:613–622
4. Scherer SS, Salzer JL (1996) Axon-Schwann cell interactions during peripheral nerve degeneration and regeneration. In: Jessen KR, Richardson WD (eds) *Glial cell development*. Bios Scientific, Oxford, UK, pp 169–196
5. Fu SY, Gordon T (1997) The cellular and molecular basis of peripheral nerve regeneration. *Mol Neurobiol* 14:67–116
6. Brushart TM (1993) Motor axons preferentially reinnervate motor pathways. *J Neurosci* 13:2730–2738
7. Belkas JS, Shoichet MS, Midha R (2004) Peripheral nerve regeneration through guidance tubes. *Neurol Res* 26:151–160
8. Li H, Terenchi G, Hall SM (1997) Effects of delayed re-innervation on the expression of c-erb receptors by chronically denervated rat Schwann cells in vivo. *Glia* 20:333–347
9. Dedkov EI, Kostrominova TY, Borisov AB, Carlson BM (2002) Survival of Schwann cells in chronically denervated skeletal muscles. *Acta Neuropathol (Berl)* 103:565–574
10. McKenzie IA, Biernaskie J, Toma JG, Midha R, Miller FD (2006) Skin-derived precursors generate myelinating Schwann cells for the injured and dysmyelinated nervous system. *J Neurosci* 26:6651–6660

Peripheral Nervous System (PNS)

Definition

Peripheral Nervous System (PNS) is part of the vertebrate nervous system comprised of the nerves outside of the central nervous system and including cranial, spinal nerves and sympathetic and parasympathetic systems.

Peripheral Neurons

Definition

Motor, sensory and autonomic neurons with axons that connect the body to the central nervous system (brain, spinal cord).

► [Peripheral Nervous System](#)

Peripheral Neuropathies

Definition

Peripheral neuropathies are diseases of peripheral nerves and can occur in acute and chronic forms. Often motor and sensory fibers are afflicted together. Motor symptoms include muscle weakness and depression or loss of tendon reflexes. Sensory symptoms vary and may include ► [paresthesias](#) such as numbness, pins-and-needles sensations, tingling, impaired cutaneous pain and temperature sensations (with risk of injuries), varied impairment of cutaneous mechanical sensation and ► [proprioception](#). Often, peripheral body parts are involved most strongly, leading to the so-called glove-and-stocking pattern. There is a specific form of ► [large-fiber sensory neuropathy](#).

► [Tendon reflex](#)

Peripheral Oscillator

ACHIM KRAMER

Laboratory of Chronobiology, Charité
Universitätsmedizin Berlin, Berlin, Germany

Synonyms

Peripheral clock

Definition

The term “peripheral oscillator” refers to a circadian oscillator, which is located in cells, tissues or organs outside of the suprachiasmatic nucleus (the site of the master oscillator in mammals).

Characteristics

Properties

In mammals, the circadian system is organized in a hierarchical manner. In addition to the ► [master clock](#) in the ► [suprachiasmatic nucleus](#) (► [SCN](#)), peripheral tissues (such as liver, kidney, heart, skeletal muscle etc.), some extra-SCN neuronal tissues (such as the olfactory bulb) as well as even some immortalized cell lines (e.g. rat-1 and NIH3T3 fibroblasts [1]) exhibit circadian gene expression. The molecular mechanism of these ► [oscillations](#) is similar to that in the SCN [2].

Peripheral oscillators are cell-autonomous and ► [self-sustained](#), but – in contrast to ► [cellular clocks](#) in SCN neurons – probably not synchronized within a tissue. Therefore, explants of peripheral tissues display

damped oscillations on the tissue-level *ex vivo* with self-sustained, but gradually desynchronizing individual **▶cellular oscillators** [3].

In vivo, peripheral oscillations **▶phase-lag** the rhythms in the SCN by several hours and are dominated by the circadian **▶pacemaker** in the SCN (master-slave oscillators). For example, embryonic fibroblasts from **▶Period1**-deficient mice (which have an **▶endogenous period** of 20 h) exhibit wild-type period oscillations when implanted in wild-type mice [4].

Function

Peripheral oscillators are thought to regulate **▶circadian** rhythms in local physiology. Genome-wide transcriptional profiling of various peripheral tissues revealed that about 5–10% of all mRNAs show a circadian expression pattern. Interestingly, while rhythmic transcripts expressed in many or all peripheral tissues are rare (they include components of the core oscillator machinery), the majority of oscillating transcripts are either only expressed or only rhythmic in one particular tissue. In the liver, for example, some of these rhythmic genes code for enzymes involved in rate-limiting steps of rhythmic hepatocytic processes suggesting that these rhythms are generated by a local liver oscillator.

Formally, however, it is difficult to decide whether a tissue-specific rhythm is regulated by a peripheral oscillator or driven by rhythmic systemic factors or by a combination thereof. To investigate these possibilities, tissue-specific clock knockout mice have been investigated. In the liver, for example, the majority of rhythmic transcripts are only rhythmic when the liver clock is functioning. A small fraction of transcripts (including *Period2*), however, continue to oscillate without a functional liver clock suggesting that these rhythms are driven by systemic circadian cues [5]. In the **▶retina**, the local clock seems to be required for a normal physiology of vision. It regulates both the rhythmic expression of genes in a **▶light-dark cycle** that are not rhythmic in **▶constant conditions** as well as inner retinal electrical responses to light [6]. In the heart, disruption of the local clock leads to a severely attenuated induction of myocardial fatty acid-responsive genes during fasting [7]. Together, these results indicate that peripheral clocks significantly contribute to important physiological functions *in vivo*.

The circadian expression of genes within a given tissue is often widely distributed among circadian phases. This ensures that within a single cell biochemically incompatible processes are separated in time. Molecularly, different phases of expression can be regulated in various ways: the expression of so-called first-order **▶clock-controlled genes** is directly regulated by components of the core oscillator. These rhythmic gene products themselves can regulate rhythmic processes further

downstream, which may even be tissue-specific. Thereby, a complex hierarchy of rhythmic expression patterns with varying phases may emerge regulating the rhythmic physiology specific for a given tissue.

Entrainment

While the SCN clock is synchronized to the geophysical time (**▶entrainment**) by light-dark cycles, peripheral cells of mammals are not light-sensitive. Hence, daily **▶non-photic resetting** cues are required for a correct phase relation among SCN and peripheral tissues. Up to now, the identity of these cues is unknown, although it is likely that many factors contribute to the entrainment of peripheral oscillators. Humoral as well as neuronal signals emanating from the SCN have been suggested to entrain peripheral oscillators. There are neural outputs from the SCN to peripheral organs via the autonomic nervous system, indicating direct (multisynaptic) neural control. Glucocorticoid hormones are prominent candidate factors, since (i) they are able to strongly phase-shift peripheral oscillators both *in vitro* and *in vivo* and (ii) the SCN regulates the rhythmic expression of glucocorticoid hormones *via* the hypothalamic-pituitary-adrenal axis. In addition, several more indirect routes are discussed to be involved in the daily resetting of peripheral oscillators. (i) The SCN directly regulates daily activity-rest cycles and thus also rhythmic food consumption. While feeding time has almost no effect on the SCN clock, peripheral oscillators are strongly influenced by restricted feeding schedules [8]. If food is available only in the inactive phase, the molecular circadian clock in the periphery is completely uncoupled from the SCN and synchronizes to the restricted feeding rhythm (see also: **▶food entrainable oscillator**). It has therefore been speculated that peripheral clocks sense the metabolic state, which would impinge on the molecular properties of the cellular oscillator and thereby phase-reset the molecular clock [9]. (ii) The circadian clock in the SCN regulates rhythmic fluctuations in core body temperature. These temperature rhythms are sufficient to entrain cultured fibroblasts [10]. Thus, it is conceivable that body temperature rhythms contribute to the entrainment of peripheral oscillators. Together, it seems likely that a variety of pathways are involved in the daily entrainment of peripheral oscillators, and different tissues may require different resetting cues.

References

1. Balsalobre A, Damiola F, Schibler U (1998) A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* 93:929–937
2. Yagita K, Tamanini F, van Der Horst GT, Okamura H (2001) Molecular mechanisms of the biological clock in cultured fibroblasts. *Science* 292:278–281

3. Nagoshi E, Saini C, Bauer C, Laroche T, Naef F, Schibler U (2004) Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. *Cell* 119:693–705
4. Pando MP, Morse D, Cermakian N, Sassone-Corsi P (2002) Phenotypic rescue of a peripheral clock genetic defect via SCN hierarchical dominance. *Cell* 110:107–117
5. Kornmann B, Schaad O, Bujard H, Takahashi JS, Schibler U (2007) System-driven and oscillator-dependent circadian transcription in mice with a conditionally active liver clock. *PLoS Biol* 5:e34
6. Storch KF, Paz C, Signorovitch J, Raviola E, Pawlyk B, Li T, Weitz CJ (2007) Intrinsic circadian clock of the Mammalian retina: importance for retinal processing of visual information. *Cell* 130:730–741
7. Durgan DJ, Trexler NA, Egbejimi O, McElfresh TA, Suk HY, Petterson LE, Shaw CA, Hardin PE, Bray MS, Chandler MP, Chow CW, Young ME (2006) The circadian clock within the cardiomyocyte is essential for responsiveness of the heart to fatty acids. *J Biol Chem* 281:24254–24269
8. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U (2000) Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev* 14:2950–2961
9. Rutter J, Reick M, Wu LC, McKnight SL (2001) Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science* 293:510–514
10. Brown SA, Zumbrunn G, Fleury-Olela F, Preitner N, Schibler U (2002) Rhythms of mammalian body temperature can sustain peripheral circadian clocks. *Curr Biol* 12:1574–1583

Peripheral Proteins

Definition

Protein molecules that are anchored to either the cytoplasmic or extracellular side, such as intracellular signaling components, immunoglobulins and structural proteins.

► Membrane Components

Peripheral Receptor

Definition

The peripheral receptor is the junction site of peripheral autonomic nerve terminals on target organs. Receptors of sympathetic nerves contain noradrenaline (norepinephrine), except sweat glands, as neurotransmitter.

These include adrenergic α and β receptors. Receptors of sweat glands contain acetylcholine as a neurotransmitter. Parasympathetic nerve receptors contain acetylcholine as a transmitter.

- Acetylcholine
- Noradrenaline
- Parasympathetic Pathways
- Sympathetic Pathways

Peripheral Rhythms

Definition

Circadian rhythms of molecular, physiological or behavioural parameters, which are generated in cells, tissues or organs outside of the suprachiasmatic nucleus (the site of the master oscillator in mammals).

- Circadian Rhythm
- Clock Coupling Factors
- Suprachiasmatic Nucleus

Peripheral Sensitization

Definition

Sensitization of nociceptors for mechanical, thermal and chemical stimuli.

- Hyperalgesia and Allodynia
- Joint Pain

Peripheral Synapse

Definition

A synapse that is located outside of the central nervous system. An example of a peripheral synapse is the neuromuscular junction where axons of motoneurons synapse with muscle fibers. Another example is the myenteric plexus of the enteric nervous system.

- Neuromuscular Junction (NMJ)

Peripheral Vestibular Apparatus

J. DAVID DICKMAN

Department of Anatomy and Neurobiology,
Washington University, St. Louis, MO, USA

Definition

The *peripheral vestibular apparatus* detects head motion and position of the head in space relative to gravity. Motion detection and our sense of position in space are determined by receptors of the vestibular system that lie in the inner ear. Although not considered to be a cognitive sense, the vestibular system nonetheless contributes to the fine control of visual gaze, posture, spatial orientation and navigation. Here the peripheral receptor apparatus and its role in motion detection and spatial orientation is discussed.

Characteristics

Structure of the Peripheral Vestibular Sensors

In every day life, two types of motion, rotational and linear are experienced. Orientation relative to gravity is constantly updated. Rotational motion (*angular acceleration*) is experienced during head turns, while *linear acceleration* occurs during walking, falling, leaning and during vehicular travel. *Linear accelerations* are also experienced during head tilts relative to gravity. Detection of motion and spatial position begins with the vestibular receptors lying in the inner ear. These receptors then send this information to the brain, where it is integrated into a uniform signal regarding direction and speed of motion, as well as the position of the head in space. In the brain, signals from vestibular receptors combine with information from other systems detecting motion such as the muscle proprioceptors and visual receptors. Central processing of these multimodal signals occurs very rapidly to ensure adequate coordination of visual gaze and postural responses (balance), autonomic responses and awareness of spatial orientation.

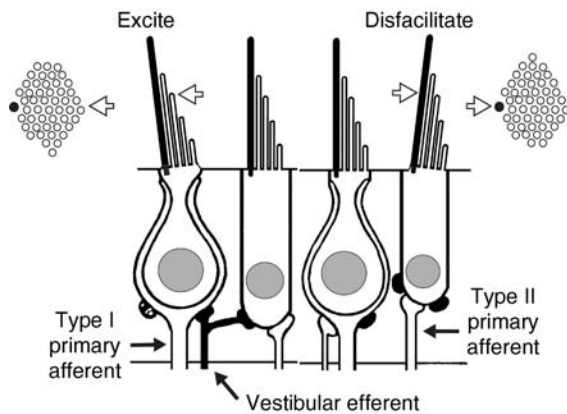
Vestibular Labyrinth

The vestibular labyrinth of the inner ear is located in the temporal bone, lateral and posterior to the cochlea. It consists of two parts. The *bony labyrinth* houses and protects the more fragile sensory structures contained inside the *membranous labyrinth*. Five separate receptor structures are represented in the vestibular portion of the membranous labyrinth. These include *three* ▶**semicircular canals** and *two* ▶**otolith** organs. The five vestibular receptor organs on each side of the head complement each other in function. The three semicircular canals, including the horizontal, anterior and posterior canals, lie in three different head planes and respond to rotational head movements [1]. The two

otolith organs, including the ▶**utricle** and ▶**sacculle**, perceive linear motions of the head (*linear accelerations*) and the orientation of the head relative to gravity [2]. Each of the semicircular canals and otolith organs are spatially aligned so as to be maximally sensitive to movements in specific directions. For example, the horizontal semicircular canal and the utricle both lie in a plane roughly equivalent to that of the head held during normal walking posture. In humans, that plane lies about 30° elevated from the naso-occipital axis. In contrast, the vertical canals and the sacculle lie in vertical head planes, nearly orthogonal to the horizontal semicircular canal. Each of the canals on one side of the head works in opposite fashion to their counterparts in the contralateral ear. Together, receptors inside the semicircular canals and otolith organs can respond to head motion in any spatial direction. The membranous labyrinth consists of a series of fluid-filled tubes and sacs where the mechanics of motion detection and transduction occur. Surrounding the membranous labyrinth is a fluid called ▶**perilymph**. It is similar to cerebral spinal fluid and has a high concentration of sodium. Inside the membranous labyrinth, where the vestibular receptors lie is a very different fluid called ▶**endolymph**, which is similar to intracellular fluid, with a high concentration of potassium. Endolymph is important, because it is the high potassium concentration that drives transduction of the motion detection mechanoreceptors. The receptor cells of the vestibular organs are innervated by primary afferent neurons that make up part of the *vestibulocochlear* or *VIIIth cranial nerve*. The somas of these bipolar afferents lie in the vestibular ganglion (Scarpa's ganglion) nestled in the internal *acoustic meatus*, a small shelf-like opening through which axons from the ganglion pass into the ipsilateral brainstem, cerebellum and reticular formation.

Hair Cells

Motion detection begins with mechanoreceptor cells in the vestibular system called ▶**hair cells** due to the many ▶**stereocilia** that project from the apical portion of the receptor cell. Each hair cell contains 50–100 stereocilia and a single longer ▶**kinocilium**. The stereocilia are oriented in a number of rows of ascending height, where the tallest stereocilia lie next to the kinocilium. There are two types of hair cells that differ in their morphology, afferent terminations and channel currents. Type I hair cells look like chalices (Fig. 1). They are completely surrounded by a unique calyx-shaped afferent terminal [3]. These type I hair cells are characterized by an inward-rectifying potassium current. Type II hair cells are cylindrically shaped and are innervated by simple synaptic boutons from the vestibular afferent fibers. Both types of hair cells exhibit excitatory synapses upon VIIIth nerve afferents, with glutamate or aspartate as the neurotransmitter. Both types of hair



Peripheral Vestibular Apparatus. Figure 1 Schematic of hair cells. Type I hair cells have a calyx-like form that is encapsulated by a primary afferent. Type II hair cells have a cylindrical form. The hair cell bundles contain a single kinocilium (black) and multiple stereocilia (clear). The open arrows indicate a deflecting force applied to hair cell bundles. To the left, the Type I hair cell bundle is deflected in towards the kinocilium, exciting the hair cell, increasing release of transmitter (aspartate or glutamate) and increasing the discharge of the vestibular primary afferent. To the right, the Type II hair cell bundle is deflected away from the kinocilium, disfacilitating the hair cell, decreasing release of transmitter and decreasing the discharge of the vestibular primary afferent. Vestibular efferents (illustrated in black) synapse on the primary vestibular afferents of Type I hair cells and directly on Type II hair cells.

cells also receive vestibular efferent input (acetylcholine, calcitonin gene-related peptide) from the brainstem, which is believed to be involved in controlling receptor sensitivity.

For each of the semicircular canals, the receptor hair cells lie in a specialized patch of neuroepithelium termed the *crista*. The *crista* is contained in an enlarged region of the membranous duct termed the **▶ampulla**, in the approximate center of the canal. A gelatinous structure, termed the **▶cupula**, completely covers the *crista* and forms a fluid-tight partition across the ampulla. The stereocilia of the hair cells are embedded in the gelatinous cupula. During rotational head movements, endolymph is displaced (lags behind) inside the membranous ducts due to inertia and pushes the cupular partition in a direction opposite to the head turn. In each of the three semicircular canals, the hair cells have a uniform anatomical orientation. In each hair cell the kinocilium and stereocilia have the same spatial polarization. Cupular movement causes the stereocilia and kinocilium to flex towards or away from each other. When the stereocilia bend towards the kinocilium, an excitatory generator potential is produced (see below). When they bend away from the kinocilium, hair cells become less polarized. The anatomical polarization

of hair cells within a particular semicircular canal gives rise to the directional selectivity of each vestibular organ.

Linear accelerations are detected by receptor hair cells in the otolith organs, which lie in a specialized neuroepithelium termed the *macula*. The stereocilia of the otolith hair cells extend into a gelatinous coating above the macula that is covered by thousands of calcium carbonate crystals, termed **▶otoconia** (Greek for ear stones). The otoconia, being much more dense than the surrounding endolymph are not displaced by normal endolymph movements, but instead are only moved during linear motion or changes in head position relative to gravity (linear accelerations) due to their inertia. These otoconia displacements produce bending of the underlying hair cell stereocilia.

Mechanoelectric Transduction

Motion detection begins with the receptor hair cells, which are directionally selective to stereocilia displacement. With movements of the stereocilia towards the kinocilium, hair cell membranes are depolarized and the innervating vestibular afferent fibers increase their firing rate. However, if the stereocilia are deflected away from the kinocilium, the hair cell is hyperpolarized and the afferent fibers decrease their firing rate. This works through *mechanoelectric transduction* of specific potassium (K^+) channels in the apical portion of the kinocilium [4]. When the stereocilia are deflected toward the kinocilium, small actin filaments open the potassium channels, allowing K^+ to enter the hair cell (due to concentration gradients from the endolymph) and depolarize the cell membrane. Through a cascade of events, depolarization leads to synaptic vesicle and neurotransmitter (aspartate or glutamate) release. The transmitter binds with excitatory receptors in the post-synaptic terminal of the vestibular afferent, depolarizing the afferent and increasing its action potential firing rate. When the kinocilium and stereocilia are returned to their normal positions, voltage sensitive potassium channels at the base of the hair cell are allowed to open and release K^+ , thereby repolarizing the membrane to its resting potential. When the stereocilia are deflected away from the kinocilium, more potassium channels close and further release of K^+ through the basolateral potassium channels occurs, resulting in cell hyperpolarization. When the head is stationary, vestibular primary afferent fibers have a high spontaneous firing rate (approximately 90 impulses/s). The high rate allows for bidirectional response of the afferents so that silencing (rectification) of the neural response to most natural head motions does not occur.

Morphological Polarization of Hair Cells

Since the hair cells are directionally selective, their orientation on the *cristae* and *maculae* are important for signaling direction of movement. For example, all

hair cells in the horizontal semicircular canal cristae are arranged similarly, with their kinocilium lying closest to (i.e. pointing toward) the utricle. Horizontal head rotations that produce endolymph movement toward the utricle causes deflections of the stereocilia towards the kinocilium and all of the hair cells in the horizontal semicircular canal are depolarized. Since all hair cells in each of the semicircular canals have the same anatomical orientation, the geometry of the canals determines directional selectivity (Fig. 2a).

The kinocilia of utricular hair cells are oriented towards an imaginary line that runs through the center of the utricular macula. This imaginary line corresponds to a physical structure termed the ▶striola, a dense pile of small otoconia on the surface membrane of the macula. (Fig. 2c). On either side of the striola the kinocilium-stereocilia axes are oppositely polarized. The hair cells in the saccular macula have a similar polarization on opposite sides of the striola (Fig. 2b).

Hair cells in the utricular macula encode linear acceleration in the horizontal plane. Hair cells in the saccular macula encode linear acceleration in the vertical plane. However, since both the saccular and utricular maculae have curved surfaces and since the striola is also curved, linear motions along any direction in three-dimensional space will excite a subpopulation of hair cells.

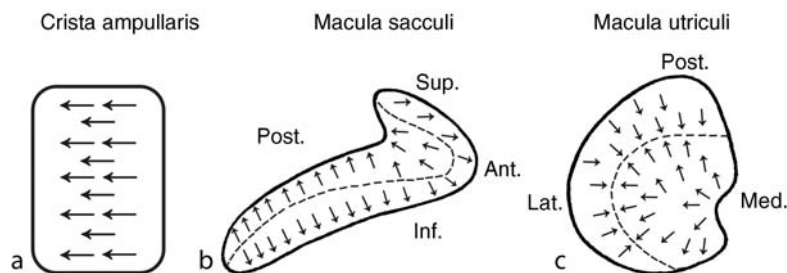
Semicircular Canal Function

The membranous semicircular duct consists of a fluid-filled tube with a partition (the cupula) in the middle. When the head is stationary, no rotational acceleration is imparted to the semicircular canals and no endolymph flow occurs. The afferents from the complementary canals on both sides of the head have nearly equivalent firing rates. When the head turns, say about the vertical axis, as in shaking the head to indicate “no,” the horizontal semicircular canals turn with it,

leaving the endolymph fluid behind (lagging the duct) due to inertial forces and viscous drag between the fluid and the walls of the canals. The relative endolymph movement on one side of the head pushes the cupula partition and produces stereocilia deflection towards the kinocilium, while the endolymph movement on the opposite side causes stereocilia deflection away from the kinocilium. Depending upon the direction (toward/away from the kinocilium) stereocilia deflection elicits either depolarization or hyperpolarization of the hair cell membrane. With a leftward head turn, the stereocilia in the left horizontal semicircular canal will be deflected toward the kinocilium resulting in increased discharge of the left VIIIth nerve afferents. Conversely, the right horizontal canal hair cells will be hyperpolarized, since the stereocilia are deflected away from the kinocilium, producing decreased firing rates in right VIIIth nerve fibers. With a rightward head turn, the opposite activation pattern in the hair cells and afferents will be produced.

This functional coupling of the two horizontal semicircular canals also applies to pairs of vertical semicircular canals. For example, the left posterior semicircular canal lies in roughly the same plane as the right anterior semicircular canal. When the head is moved in an angle of about 45° off an imaginary sagittal plane through the head, the discharge from afferents of one of these vertical canals increases and the discharge from the other decreases.

Neural information carried on vestibular afferent fibers from both the left and right semicircular canals is transmitted into the vestibular nuclei. Many neurons in the vestibular nuclei receive information from receptors on both sides of the head, so that coding of rotation direction can be very precise. Due to the mechanics of the semicircular canal system, as well as the transduction properties of pre- and post-synaptic processing, semicircular canal afferents encode head velocity and



Peripheral Vestibular Apparatus. Figure 2 Hair cell polarization a semicircular canal crista and in saccular and utricular maculae. Hair cell polarization is indicated by the orientation of the multiple stereocilia with respect to the single kinocilium. (a) In a semicircular canal crista ampullaris the polarization of hair cells is uniform as indicated by the alignment of the arrows. (b) The polarization of hair cells in the saccular macula is opposite on either side of the dividing line that corresponds to the striola, indicated by the dashed line. Note that the saccular macula is aligned with the sagittal plane. (c) The polarization of hair cells in the utricular macula is also opposite on either side of the striola. The predominant polarization of hair cells in the utricular macula is mediolateral.

are band limited in their response to motion. Very slow head rotations (e.g. less than 3–4°/s) produce little response. Instead, afferents are most responsive to rotation speeds between 10 and 150°/s [5], which is in the most often produced range of human head movements.

Otolith Function

Linear motion or changes of head position with respect to gravity (rolled or pitched) causes otoconial displacement due to inertia and consequent deflection of stereocilia in otolithic hair cells. Similar to semicircular canal receptors, otolith hair cells are either depolarized or hyperpolarized by stereocilial deflection toward or away from the kinocilium. Thus, a topographic coding of directional space or movement is represented by the activation of hair cells in particular regions of the maculae. The innervating VIIIth nerve fibers maintain the directional signal, since each afferent only innervates hair cells from a small region on the macular neuroepithelium. Unlike semicircular canal afferents, otolith afferents respond to static head positions, slow head movements, fast head movements and even very fast vibrations with high fidelity.

Vestibular Efferent System

Hair cells and vestibular primary afferents receive information from the brain conveyed by vestibular efferents. The vestibular efferent system (VES) consists of a group of 100–500 cells bordering the genu of the facial nerve in the dorsal brainstem whose axons terminate on vestibular primary afferents and hair cells in the labyrinth [6,7]. Neurons of the VES are cholinergic, identified by acetylcholinesterase histochemistry [7] and choline acetyltransferase immunohistochemistry [8] as well as by the retrograde transport of [³H]-choline.

The functional importance of the VES has remained an enigma because of the technical difficulty of physiologically identifying putative neurons of the VES and analyzing the response characteristics of these neurons *in vivo*. In fish, vestibular efferents can be identified physiologically and intracellularly labeled [9]. In the chinchilla, indirect evidence suggests that vestibular efferents receive vestibular inputs from both the ipsilateral and contralateral labyrinths.

In the cat and the monkey, it is possible to study the action of the VES indirectly by electrically stimulating the region of the brain stem where the cell bodies of vestibular efferents are located and simultaneously recording the effect on the activity of single primary afferents [6]. Primary vestibular afferents in both the fish and the monkey are excited by electrical stimulation of vestibular efferents [6,9].

Two similar ideas have been proposed to explain the function of the VES. (i) Vestibular efferents are used to establish an operating point on the sensitivity curve

for primary vestibular afferents so that in different vestibular environments these afferents can be modulated within a linear range [6] and (ii) vestibular efferents detect behavioral arousal and thereby lower the threshold of vestibular primary afferents, thereby facilitating guidance of escape behaviors [9]. Implicit in these two ideas is the necessity of a central correlative efferent signal, so that changes in primary afferent activity induced by vestibular efferent signals can be distinguished from changes in primary afferent activity caused by peripheral vestibular stimulation. Such modifications could take tens of milliseconds or tens of minutes.

Regeneration of Hair Cells

Remarkably, in many vertebrates including amphibians, reptiles and birds, hair cells and their innervating afferents spontaneously regenerate [10]. Spontaneous *regeneration* of mammalian hair cells does not occur. However, recent developments in promoting mammalian regeneration provide renewed hope for restoring hearing and balance following hair cell loss.

References

1. Fernandez C, Goldberg JM (1971) Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey. II. Response to sinusoidal stimulation and dynamics of peripheral vestibular system. *J Neurophysiol* 34:661–675
2. Fernandez C, Goldberg JM (1976) Physiology of peripheral neurons innervating otolith organs of the squirrel monkey. I. Response to static tilts and to long-duration centrifugal force. *J Neurophysiol* 39:970–984
3. Lindeman HH (1973) Anatomy of the otolith organs. *Adv Otorhinolaryngol* 20:405–433
4. Hudspeth AJ (2005) How the ear's works work: mechanoelectrical transduction and amplification by hair cells. *C R Biol* 328:155–162
5. Hullar TE, Della Santina CC, Hirvonen T, Lasker DM, Carey JP, Minor LB (2005) Responses of irregularly discharging chinchilla semicircular canal vestibular-nerve afferents during high-frequency head rotations. *J Neurophysiol* 93:2777–2786
6. Goldberg JM, Fernandez C (1980) Efferent vestibular system in the squirrel monkey: anatomical location and influence on afferent activity. *J Neurophysiol* 43:986–1025
7. Warr WB (1975) Olivocochlear and vestibular efferent neurons of the feline brain stem: Their location, morphology and number determined by retrograde axonal transport and acetylcholinesterase histochemistry. *J Comp Neurol* 161:159–181
8. Schwarz DWF, Satoh K, Schwarz IE, Hu K, Fibiger HC (1986) Cholinergic innervation of the rat's labyrinth. *Exp Brain Res* 64:19–26
9. Highstein SM, Baker R (1985) Action of the efferent vestibular system on primary afferents in the toadfish, *Opsanus tau*. *J Neurophysiol* 54:370–384
10. Zakir M, Dickman JD (2006) Regeneration of vestibular otolith afferents after ototoxic damage. *J Neurosci* 26:2881–2893

Peripheral Vision

Definition

Vision excluding the 5°–10° most central area of the visual field (foveal and peri-foveal vision). Peripheral vision is specialized for low spatial frequency and high temporal frequency stimuli, is not sensitive to wave-length (achromatic) and has a low sensitivity/rapid adaptation to light intensity (scotopic).

► Visual Field

Peristalsis

Definition

Peristalsis is the propagating contraction of the circular muscle layer of the bowel. The contractions develop into peristaltic waves moving along the gut and provide the forces for propelling bowel contents usually in an aboral direction. The peristaltic waves occur intrinsically at a frequency of 3 per/min, but they usually travel only a short distance.

Peristalsis in the Small Bowel

Definition

Peristalsis is the propagating contraction of the circular muscle layer. The contractions develop into peristaltic waves moving along the gut and provide the forces for propelling bowel contents usually in an aboral direction.

The peristaltic waves occur intrinsically at the frequency of 3/min, but they usually travel only a short distance.

► Bowel Disorders

Peristimulus Time Histogram (PSTH)

Definition

Cumulative histogram of the number of spikes occurring within discrete time bins in and around the time of a repeated presentation of an auditory stimulus.

Perisynaptic Schwann Cells

Definition

Schwann cells normally encase axons in peripheral nerves to form the insulating myelin sheath. At the neuromuscular junction between the motor nerve and the endplate region of each skeletal muscle cell, there are Schwann cells that do not form myelin but normally respond to the chemical neurotransmitter substance, acetylcholine, that is released from active nerve terminals to excite the skeletal muscle fibers and in turn, lead to muscle contraction. These Schwann cells are termed perisynaptic Schwann cells because they are at the synaptic region of each muscle fiber.

- Acetylcholine
- Axonal Sprouting in Health and Disease
- Myelin
- Schwann Cell

Periventricular Zone

Definition

The periventricular region of the thalamus has poorly-defined cell groups that are sometimes homologized with the midline thalamic groups seen in non-primates such as nucleus reunions, rhomboid nucleus, and median central nucleus. It is likely that the region is involved in visceral activities in that it has connections to the hypothalamus, amygdala, and cingulate cortex.

Permeabilized Skeletal Muscle Fibers

Definition

Experimental model using single muscle fibers after membrane destruction via detergents or other means. Membrane destruction renders the contractile proteins actin and myosin directly accessible to the external media.

► Force Potentiation in Skeletal Muscle

Per-Rotatory Vestibular Nystagmus

Definition

Nystagmus produced during prolonged rotation of the head in space. For rapid initiation of rotation, the slow phase velocity rises sharply at the start of rotation and declines to zero as the rotation continues at a constant velocity.

► Nystagmus

Persephin

Definition

A member of the glial cell line-derived neurotrophic factor (GDNF) family of neurotrophic factors that also includes artemin and neuroturin. GDNF family members use a receptor complex that consist of the common receptor tyrosine kinase signaling component Ret and one of the GPI-linked receptors (GFR α 1 to 4) that regulate ligand binding specificity. GFR α 4 is the preferred receptor for persephin.

► Neurotrophic Factors in Nerve Regeneration

Persistent Na⁺ Currents

Definition

Persistent Na⁺ currents are TTX-sensitive, voltage-dependent Na⁺ currents flowing at voltages between −65 and −40 mV, and thus significantly influencing sub-threshold membrane potential changes and the firing rate and pattern of discharge.

► Action Potential
► Sodium Channels
► Tetrodotoxin

Persistent Vegetative State

Definition

This state results from damage of cortical neurons (particularly ► pyramidal cells) in ► hippocampus and

► cerebral cortex after prolonged hypoxia or ischemia. One to two weeks of coma may be followed by a state similar to that of ► hydrocephalic children, in which patients appear awake, may smile, cry, fixate objects, or eat food put in their mouth, but have no cognitive relation to their environment.

Personal Knowledge

Definition

Personal knowledge is knowledge possessed by a person (not for example by a scientific community or culture etc.).

► Knowledge

Personality Disorder

ANNETTE BÖLTER, JÖRG FROMMER
Universitätsklinikum Magdeburg, Abteilung für
Psychosomatische Medizin und Psychotherapie,
Magdeburg, Germany

Synonyms

Character neurosis; Characterogenic neurosis; Auto-psychic neurosis; Psychopathic personality

Definition

A heterogeneous group of disorders, regarded as long-standing, pervasive, inflexible and maladaptive personality traits, patterns of behavior and thinking that impair social and occupational functioning.

Characteristics

Personality disorders are coded on Axis II of DSM. They are often comorbid with an Axis I disorder and can serve as a context for Axis I problems, for example depression or anxiety disorder, shaping them in different ways. The symptoms come close to describing characteristics that all people possess from time to time and in varying degrees, however the diagnoses of a personality disorder is defined by the extremes of several traits and is not used unless the patterns of behavior are enduring, pervasive and dysfunctional.

Beside personality disorders DSM-IV distinguishes personality change, for example after a major medical condition. Five subtypes of personality change are listed: labile, disinhibited, aggressive, apathetic and paranoid.

Categories and Clusters of Personality Disorders

DSM-IV distinguishes ten subgroups: (i) Paranoid, (ii) Schizoid, (iii) Schizotypal, (iv) Borderline, (v) Histrionic, (vi) Narcissistic, (vii) Antisocial, (viii) Dependent, (ix) Avoidant, (x) Obsessive-compulsive (**►Obsessive-Compulsive Disorder [OCD]**). In DSM-IV these subtypes are also grouped into three clusters: Cluster A (paranoid, schizoid, schizotypal) is defined by characteristics of being odd or eccentric. Because the symptoms of these disorders are similar to those of the prodromal or residual phases of schizophrenia, they are considered by some researchers to be less severe variants of schizophrenia. Individuals in cluster B (antisocial, borderline, histrionic and narcissistic) appear dramatic, emotional or erratic. Those in cluster C (avoidant, dependent and obsessive-compulsive) seem anxious or fearful.

Diagnosis

Although there do exist some diagnostic questionnaires, personality disorders are preferably assessed by structured interviews. In recent years these diagnoses have become reliable in some degree. But it is still usual for a disordered person to meet diagnostic criteria for more than one personality disorder. The categorical diagnostic system of DSM-IV therefore may not be ideal for classifying personality disorders. A dimensional approach may be more appropriate. During recent years different contributions on personality disorders emerged from several psychological paradigms: understanding on the basis of modern psychoanalysis and attachment theory, approaches based upon the five-factor model of personality, cognitive theories and Linehan's behavioristic approach, interpersonal concepts as shown by Benjamin, neurobiological models, and a self-developed approach focusing on private theories of the patients themselves.

Therapy

A therapist who is working with patients that have a personality disorder is typically also concerned with Axis I problems because most patients even enter treatment because of Axis I disorder. For example, a person with avoidant personality disorder may be seen for social phobia. Psychodynamic therapy of personality disorders has a long tradition. It aims to remove repressions and to correct the problems underlying the personality disorder. Transference-Focused Psychotherapy as developed by Kernberg is a psychodynamic

treatment designed especially for patients with severe personality disorders, e.g. **►borderline personality disorders**. The focus of treatment is on a deep psychological make up – a mind structured around a fundamental split that determines the patient's way of experiencing self and others and the environment. Since this internal split determines the nature of the patient's perceptions, it leads to the chaotic interpersonal relations, impulsive self-destructive behaviors, and other symptoms. The core task in Transference-Focused Psychotherapy is to identify the patient's moment-to-moment experience of the therapist because it is believed that the patient lives out his/her predominant object relation patterns in the patient-therapist-relationship. Another successful approach is Dialectical Behavior Therapy as developed by Linehan. During individual and group therapy, therapist and client work towards improving skill use. These skills are broken down into four modules: mindfulness (derived from Zen tradition), interpersonal effectiveness, distress tolerance, and emotion regulation. In addition common treatments of personality disorder are psychopharmacological drugs. The choice is determined by the associated Axis I disorder.

References

1. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, DSM-IV. American Psychiatric Association, Washington
2. Costa PT, Widiger TA (eds) (1993) Personality disorders and the five-factor model of personality. American Psychological Association, Washington
3. Frommer J, Reissner V, Tress W, Langenbach M (1996) Subjective theories of illness in patients with personality disorders *Psychother Res* 6:56–69
4. Kernberg OF (1984) Severe personality disorders: psychotherapeutic strategies. Yale University Press, New Haven
5. Lenzenweger MF, Clarkin JE (2005) Major theories of personality disorders, 2nd edn. Guilford Press, New York
6. Linehan MM (1993) Cognitive-behavioral treatment of borderline personality disorder. Guilford Press, New York
7. Millon T (1996) Disorders of personality: DSM-IV and beyond, 2nd edn. Wiley, New York
8. Yeomans FE, Clarkin JF, Kernberg OF (2002) A primer of transference-focused psychotherapy for the borderline patient. Jason Aronson, Northvale, NJ

Pesticide: Insecticide

►Neuroinflammation: Modulating Pesticide-Induced Neurodegeneration

PET

Definition

► Positron Emission Tomography

activities and behaviors. It might also entail enhancement of learning new information and behaviors in the adult during REM sleep.

► Rapid Eye Movement (REM) Sleep
► Sleep-Wake Autonomic Regulation

Petit Mal Seizures

Definition

► Absence Epilepsy

P23H Rat

Definition

Transgenic rat model of human Proline-23-Histidine rhodopsin mutation leading to Retinitis Pigmentosa.

► Inherited Retinal Degenerations

PFC

Definition

Prefrontal cortex.

► Prefrontal Cortex

Phagocytic

Definition

Activity of cells called phagocytes which engulfs and absorbs waste material, harmful microorganisms, or other foreign bodies in the bloodstream and tissues.

PGO Spikes

Definition

Ponto-geniculo-occipital; high amplitude sharp waves, which originate in the pons, are transmitted to the lateral geniculate and from there up to the occipital cortex, where they are recorded in cats during rapid eye movement (REM) sleep. PGO spikes reflect bursts of discharge by neurons in the pontine reticular formation which are transmitted rostrally into the visual and also other relay nuclei of the thalamus by which they are transmitted to cortical areas. This phasic activity is also transmitted to brainstem motor nuclei, as reflected in rapid eye movements, and spinal motor nuclei, as reflected in twitches of the distal extremities. Such twitches can be observed as manifestation of the phasic excitation through the brain during REM sleep which occurs in all mammals. As proposed by some, PGO spiking might signify a programming of the brain and organism during development in species-specific motor

Phantom Limb Sensation and Pain

MIKE B. CALFORD

School of Biomedical Sciences and Hunter Medical Research Institute, The University of Newcastle, Newcastle, NSW, Australia

Definition

When appropriately studied, it is usually reported that all adults who have had a limb amputated either by trauma or surgery have at some stage experienced the continued presence of the missing limb within their perceptual body image. The full range of somatosensory percepts (cutaneous touch, deep touch, vibration, itch, tickle, joint movement etc) are variously ascribed to the phantom. Attribution of pain to a phantom limb is a distinct phenomenon with widely varying reports of prevalence. Recent studies have reported higher proportions of cases with phantom limb

pain (60–80%) and there is a possibility that earlier reports were affected by patient reluctance to describe their experience.

Those with spinal cord injury (paraplegia, quadriplegia) rarely localize non-painful somatosensory percepts to their affected limbs. However they usually retain these limbs within their body image and sometimes attribute full function to them – a form of *anosognosia* also found in some cases of stroke-induced hemiplegia. There is no consensus view of the prevalence of phantom pain after spinal cord injury. This may be attributable to varying pathology and to the extent of the lesion. Irrespective of this, there are many well-described cases of phantom limb pain after complete spinal transection.

Supernumerary limb is a term that encompasses various presentations of the appearance of a third (or more) arm or leg in the perceptual body image. A similar misperception can occur temporarily with brachial plexus nerve block, but it is a rare chronic condition usually following transient middle cerebral artery ischemia or mild neurotrauma. *Alien hand* syndrome describes the converse condition in which, after mild neurotrauma, an intact limb is lost to the perceptual body image and its presence denied or disowned.

Characteristics

Phantom limb experiences manifest immediately or within a few days of an amputation. In a minority of cases, phantom sensations persist relatively unchanged. In other cases, the phantom sensations and the perceptual body image alters. With upper limb amputation, a loss of the image of the arm but retention of the phantom hand is classically described – but there are many variations. The phantom sensations disappear after a few months to years in around 50% of cases. However, in laboratory conditions with stimulation of the amputation stump (or other body parts) or with imagery, elements of a phantom limb experience can be elicited in most amputees even years after they have reported loss of the phantom sensations. Cortical activation achieved through caloric ear stimulation is reported to recall lost phantom sensations and also to alleviate temporarily painful phantom sensation by replacement with a nonpainful phantom [1].

Phantom limb pain shares many characteristics with neuropathic pain and is equally difficult to account for. Pain sensations are rarely continuous but chronic presentation of repetitive bouts is common. Phantom pain can mimic the presentation of a pre-amputation chronic pain. It is becoming widespread practice to provide limb analgesia prior to a surgical amputation. This practice has followed a number of case reports indicating that such post-amputation mimicry is thereby avoided. Nevertheless, clear evidence of efficacy for pre-surgery limb analgesia is not apparent [2].

The highly plastic nature of the somatosensory perception of the limbs can be easily demonstrated. When operating a hammer, pointer, golf club, stilts or sword, we readily telescope our body image to include the extension. In such an operation, sensory inputs from receptors in the hand or arm are combined and interpreted to provide a “percept” from the tip of the extension. While training improves performance, the extension of percept to encompass tool use by either upper or lower limb is largely automatic. In complex multisensorimotor tasks with machines (such as driving a car), we are capable of integrating a variety of somatosensory, visual and auditory cues to expand our body image to the limits of the machine or task. Within this context, it is then somewhat surprising that essentially 100% of limb amputees experience a phantom experience of their missing part, rather than adapt their body image to encompass the amputation. Nevertheless, after amputation the plastic nature of the body image is not lost, for in most cases the phantom image locks onto a prosthetic and adapts to tool use.

Melzack [3] reasoned that the perceptual experience of a limb does not derive from activation of a single brain area but from the combined output of a distributed network, termed the neuromatrix. To account for the persistent nature of phantom limb perception, in the light of considerable physiological and psychophysical evidence of plasticity, it was concluded that, when activated, elements of the overall network retain the identity of the former limb. On the basis of reports of phantom limb experiences in some cases of congenitally missing limbs, it was further suggested that the identity of a given neuromatrix is genetically predetermined. This latter suggestion remains contentious, but the broader neuromatrix concept is well accepted and is consistent with recent work.

Ramachandran and others [4,5] have described many cases in which passive cutaneous stimulation of either the amputation stump or a distant body area (e.g. face for upper limb amputation) produces a dual sensation with one being localized to the phantom. In some cases, a clear topographic map of the phantom can be plotted. These demonstrations reveal both plasticity and rigidity in the somatosensory representation of the limb consistent with the concept that some elements of the neuromatrix retain their original perceptual attribution.

Extensive plasticity of the primary somatosensory representation has been demonstrated in monkeys and other mammals. With upper limb amputation or deaf-ferentation the former arm and hand representation is taken over by a responsiveness to adjacent body areas, the back of the head and the face [6]. There is a considerable immediate unmasking effect [7] such that some areas immediately switch to show new responsiveness, but the total filling-in of the former representation develops over a longer period. The

somatosensory representation in the cortex is distributed across at least seven fields in central and parietal regions. Each is organized as a topographic map of the contralateral body and there is a partial specialization of function. Thus, for example, muscle spindles are the predominant input to one field (area 3a) while cutaneous receptors dominate others. There is, however, no cortical field devoted to or dominated by pain perception. Rather the nociceptive pathway, although separate in the spinal cord and brainstem, feeds into the major (lemniscal) somatosensory thalamocortical pathway. This may be an important aspect in any explanation of phantom limb pain, as those with persistent phantom pain could be shown with neuroimaging to have a reorganization within the primary somatosensory cortex, whereas those with an innocuous phantom did not [8]. Consistent with the reorganization reported in the monkey studies, this reorganization involved expansion of the cutaneous representation of the chin and lips into the former arm and hand area. The extent of the reorganization was highly correlated with the degree of phantom pain suggesting that activation of the cutaneous receptors of other body areas provides inappropriate stimulation to the cortical representation of the former pain signaling neurons of the missing limb. It needs to be noted that such reasoning is over simplistic if applied to any single representation since pain perception is likely to involve activation of multiple fields.

A consistent approach to managing or treating phantom pain has not developed to date. The linking of phantom pain to cortical reorganization phenomena and the knowledge that cortical representations are inherently plastic has led to investigations of potential therapies based around manipulating the reorganization, using pharmacological or physical therapy approaches [2]. Use of mirrors to aid in mental imagery to “move” the phantom limb has been reported to be successful in some cases [9]. Whereas treatments (e.g. stump analgesia) aimed at silencing a supposed overly active peripheral nerve are not generally useful, there were persistent early reports that a subgroup are helped by reducing sympathetic activity and sympathetic disturbance is often found. A plausible explanation for sympathetic activity directly affecting sensory nerves has come from animal work showing sprouting of noradrenergic sympathetic axons into the dorsal root ganglion following a peripheral nerve injury. Nevertheless, overall there is no supporting evidence for using sympathectomy as a treatment for neuropathic pain and hence for phantom pain [10].

References

- Andre JM, Martinet N, Paysant J, Beis JM, Le Chapelain L (2001) Temporary phantom limbs evoked by vestibular caloric stimulation in amputees. *Neuropsychiatry Neuropsychol Behav Neurol* 14:190–196
- Flor H (2002) Phantom-limb pain: characteristics, causes, and treatment. *Lancet Neurol* 1:182–189
- Melzack R (1990) Phantom limbs and the concept of a neuromatrix. *Trends in Neurosci* 13:88–92
- Halligan PW, Marshall JC, Wade DT, Davey J, Morrison D (1993) Thumb in cheek? Sensory reorganization and perceptual plasticity after limb amputation. *Neuroreport* 4:233–236
- Ramachandran VS, Stewart M, Rogers-Ramachandran DC (1992) Perceptual correlates of massive cortical reorganization. *Neuroreport* 3:583–586
- Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. *Science* 252:1857–1860
- Calford MB, Tweedale R (1990) Interhemispheric transfer of plasticity in the cerebral cortex. *Science* 249:805–807
- Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375:482–484
- Ramachandran VS, Hirstein W (1998) The perception of phantom limbs. The D. O. Hebb lecture. *Brain* 121:1603–1630
- Mails A, Furlan A (2003) Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev* CD002918

Phantosmia

Definition

Describes the distorted perception of smells in the absence of an odor source. Most often, phantosmias occur after trauma or URTI and consist of unpleasant odors occurring without being elicited through environmental odor sources. Phantosmias also have a tendency to disappear over the course of years.

- Smell Disorders
- Olfactory Hallucinations

Pharmacodynamics

Definition

Pharmacodynamics refers to the biochemical and physiological effects of drugs on the body.

Pharmacogenomics

Definition

The science of understanding how an organism's genetic inheritance (i.e. genotype) affects the body's response to drugs.

routine. (Lunch typically tastes better in Paris.) In order for an oscillator to entrain to signals from a pacemaker that has a shorter period, it must execute phase advances.

- ▶ Phase Advance Curve
- ▶ Oscillator
- ▶ Pacemaker

Pharmacokinetics

Definition

A branch of pharmacology that concerns itself with the process in which drug is absorbed, distributed, metabolized and eliminated by the body.

Phase Angle

Definition

The displacement, in units of time or angular degrees, between phases of two coupled oscillators, e.g., a circadian oscillator and a light-dark cycle.

- ▶ Circadian Rhythm
- ▶ Phase Advance Curve

Pharmacophore

Definition

Pharmacore is defined as a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity.

Phase Delay

Definition

A shift that sets back the time of arrival of an oscillator at a particular event marker phase. For example, flying from Paris to New York results in a 6 h phase delay of the light-dark cycle, since dusk arrives 6 h later in New York than in Paris. When people are eating supper in Paris, people in New York are eating lunch – they are at an earlier phase of their daily routine. In order for an oscillator to entrain to signals from a pacemaker that has a longer period, it must execute phase delays.

- ▶ Oscillator
- ▶ Pacemaker
- ▶ Phase Advance Curve

Phase

Definition

Any point on a cycle; the instantaneous state of a periodic process.

Phase Advance

Definition

A shift that accelerates (advances) the arrival of an oscillator at a particular event marker (phase). For example, flying from New York to Paris results in a 6 h phase advance of the light-dark cycle, since dawn in Paris is 6 h ahead of dawn in New York. When people are getting up in New York, people in Paris are eating lunch – they are already at a later phase of their daily

Phase Locking

Definition

Phase locking is a term that describes the auditory nerve's ability to discharge in synchrony with the acoustic stimulus. Auditory neurons do not fire on

every cycle of a sinusoidal acoustic sound, but rather fire stochastically on a specific phase of the stimulus.

► Cochlear Implants

Phase Locking in Auditory System

Definition

Phase locking describes the ability of a neuron to fire action potentials that are time locked to a stimulus event. In auditory neurons, phase locking is used in the context of pure tones, consisting of a single sine wave. Auditory neurons in barn owls phase lock to as high as 10 kHz, in mammals phase locking does not occur above, roughly, 4 kHz.

Phase locking requires temporal precision in action potential timing, with standard deviations of fewer than 100 μ s at some frequencies.

- Intrinsic Properties of Auditory Neurons
- Neuroethology of Sound Localization in Barn Owls

Phase Relations

Definition

Phase relations refer to the temporal relationship between coupled elements expressed as a fraction (degrees or radians) of the cycle time.

Phase Response Curve

CHRISTOPHER S. COLWELL
Department of Psychiatry, University of California,
Los Angeles, USA

Synonyms

PRC

Definition

Phase response curve (PRC) in a graph that plots the magnitude of phase shifts resulting from perturbations from discrete stimuli.

Characteristics

The discrete stimuli often come in the form of light pulses, which induce ►phase delays and ►phase advances during early and late ►subjective night, respectively, but produce negligible phase shifts during subjective day. The phases in which light does not produce a ►phase shift ($\Delta\Phi$) is referred to as the “dead zone” of the PRC. A variety of non-photoc stimuli can also generate phase-dependent phase shifts and could potentially be used to entrain the circadian system [1]. In general, these non-photoc PRCs are characterized by phase shifts during the subjective day and a dead zone during the subjective night. With both photic and non-photoc stimuli, the amplitude of the PRC can vary with the strength of the stimulus.

The most straightforward way to generate a PRC is to have a population of animals in constant conditions and to measure their ►free-running rhythms. Based on these rhythms, individual organisms can then be exposed to stimuli at discrete phases of the daily cycle and the resulting phase shifts (see definition) measured by the next cycle. By convention, phase advances are plotted as positive values while phase delays are plotted as negative values. After some perturbations (especially those that cause phase advances), there can be a few days of transients before the full magnitude of the phase shift can be determined. Under the constant conditions required for these measurements, the ►period (Tau, τ) of the rhythm will not be equal to 24-h and the phase will need to be normalized by the endogenous period. Typically, the phases of the endogenous cycle are designated as circadian time (CT) 0–24 with the number of minutes in each hour of CT being equal to Tau/24 multiplied by 60. By definition, CT 0 is the time of activity onset for a diurnal organism while CT 12 is the time of activity onset for a nocturnal one. The phases of the endogenous cycle that coincide with the prior daytime are called “subjective day” while the phases that coincide with the prior nighttime are called “subjective night”.

PRCs have been used to explain how 24-h ►entrainment is maintained between an endogenous circadian oscillator (which has a period that is not equal to 24-h) and environmental cues. While a description of this model is well beyond the scope of this article, a simple example may be useful. If the PRC is known, then the phase relationship between environment and the endogenous ►oscillator can be predicted based on the periods of the biological oscillation (Tau) and the ►zeitgeber cycle (T) [2]. For example, if the circadian oscillator has a period of 25 h and is entrained to a light pulse every 24 h. Stable entrainment can only be reached when the light causes a phase shift that corrects the difference between Tau and T which in this case would be a phase delay of 1-h per cycle ($\text{Tau} - T = \Delta\Phi$). Only when the light falls on the portion of the PRC

in the early night causing the 1-h phase delay will the biological oscillator be entrained to the physical cycle.

References

1. Johnson CH, Elliott JA, Foster R (2003) Entrainment of Circadian Rhythms. *Chronobiology International*. *Neuron* 20(5):741–774
2. Roenneberg T, Daan S, Merroa M (2003) The Art of Entrainment. *J Biological Rhythms* 18(3):183–194

Phase Shift ($\Delta\Phi$)

Definition

A shift in the phase of the biological oscillation. Phase (Φ) is one of the most important parameters describing any oscillation as it refers to the time points within the cycle. To measure the phase of the rhythm, a reliable reference point must be chosen. In the case of circadian oscillations, the onset of activity or the peak expression of a biochemical parameter are commonly used. These biological markers are typically expressed relative to the time of lights-on or lights-off when the organism is in a light cycle. For circadian oscillators, exposure to light is the most physiologically relevant and widely studied perturbation that results in phase shifts. Many treatments that cause phase shifts of the circadian system produce different effects depending on the time of day during which the treatment was applied.

- Circadian Rhythm
- Phase Response Curve

Phase Spectrum

Definition

A description of the relationship between starting phase and frequency of the sinusoidal components of a complex sound wave.

- Acoustics

Phasic

Definition

Transiently occurring at the onset or offset of an event.

Phasic responses indicate that the adaptation of the nervous system under consideration is rapid. Opposite term is tonic.

Phenethylamine

Definition

A simple molecule that serves as the framework for many biologically-active molecules, including dopamine, noradrenaline (norepinephrine), and certain hallucinogens. It is essentially a phenyl ring separated by a two carbon chain from an amino group.

- Dopamine
- Noradrenaline
- Hallucinogens

Phenomenal Character

Definition

The basic feature of many mental states to feel a certain way. It is somehow for an organism to be in pain, and it is also somehow for an organism to have a sensation of warmth. But these two mental states differ in phenomenal character in that it feels different for an organism to be in pain and to have a sensation of warmth.

- Behaviorism
- Logical

Phenomenal Concepts

Definition

Phenomenal concepts are those concepts that are immediately related to perceptions and sensations, in

such a way that one is immediately inclined to apply these concepts whenever one undergoes the appropriate experience and introspects on one's experience. Having a red experience, for example, makes one inclined to apply the phenomenal concept of a red experience.

► [The Knowledge Argument](#)

Phenomenology

Definition

“Phenomenology” means doctrine of appearances. In general it means the reflective inquiry into one's own [→] consciousness. It also names Edmund Husserl's philosophical project of studying how the world appears to us in [→] intentional consciousness. He held that intentional consciousness is intrinsically “directed” to objects. In some intentional episodes objects are merely “meant,” while in others (intuitions) objects are (partially) “given.” The “fulfillment” of the former episodes by intuitions is the basis of knowledge.

► [Argument](#)

► [Logic](#)

Phenophysics

► [Psychophysics](#)

Phenotype

Definition

Two specimens of a diploid organism, such as a flowering plant, may look alike (same phenotype), even though one is homozygous for, say, red petal color (identical alleles for the gene concerned on the two homologous chromosomes) and one is heterozygous (one allele coding for white, the other one for red which is dominant in certain plants; different genotypes).

► [Electric Fish](#)

Pheomelanin

Definition

A polymeric pigment varying in color from yellow to red and produced from 1,4-benzothiazinylalanine derived from L-tyrosine and L-cysteine by melanocytic cells.

► [Melanin and Neuromelanin in the Nervous System](#)

Pheomelanosomes

Definition

Spherical organelles 0.7 μm diameter found within melanocytes that compartmentalize pheomelanin synthesis and storage.

► [Melanin and Neuromelanin in the Nervous System](#)

Pheromone

Definition

Pheromones were originally defined in relation to insects as “substances secreted to the outside of an individual and received by a second individual of the same species in which they release a specific reaction, for example, a definite behavior or developmental process.” This led to the distinction between two categories of pheromonal effect: releaser pheromones that elicit immediate and relatively stereotyped behavioral responses, such as sexual attraction; and primer pheromones that elicit a longer-term change in hormonal or developmental state, such as acceleration of puberty. Many in the field now regard the original definition as over-restrictive and would expand the term to include signaler pheromones that convey information such as individual identity, and modulator pheromones that have an effect on mood or emotion.

► [Accessory Olfactory System](#)

► [Chemical Senses](#)

► [Evolution of Olfactory and Vomeronasal Systems](#)

Philosophy of Action

► Action, Action-Theory

Phobic Neurosis

Definition

An anxiety disorder in which there is intense fear and avoidance of specific objects or situations, most frequently fear of wide places (agoraphobia), closed spaces (claustrophobia) or animals. The fear is recognized as irrational by the individual.

► Personality Disorder

Phoneme

Definition

The minimal contrastive unit in the sound system of a language; substituting one phoneme for another changes the meaning of a word (e.g., /t/ vs. /n/ because/bat/ differs in meaning to /ban/).

Phonotaxis

Definition

Sound-induced, directional movement of an organism relative to the sound source. It is usually either directed towards the source (positive phonotaxis) or away from it (negative phonotaxis). It is most commonly found in acoustic communication behaviors in insects.

► Auditory-Motor Interactions

Phosphacan

Definition

One kind of axon growth inhibitors. It is expressed in the CNS as a secreted splice variant of the gene encoding the extracellular domain.

► Regeneration of Optic Nerve

Phosphagen

Definition

The term given to both high-energy phosphate compounds, 5'-adenosine triphosphate and phosphocreatine.

► Energy Sensing and Signal Transduction in Skeletal Muscle

Phosphatidyl Inositol-3-kinase (PI 3-kinase or PI3K)

Definition

Part of a family of related enzymes that phosphorylate the 3 position hydroxyl group of the inositol ring of phosphatidylinositol. The phosphorylated phosphoinositides produced by PI 3-kinases function via the phosphoinositide-binding domains, which are recruited to cellular membranes for various signaling functions.

PI3K and its downstream effector the actin-associating Protein kinase (Akt) pathway are involved in the regulation of neuronal soma size and axon caliber.

► Neurotrophic Factors in Nerve Regeneration

Phosphene

Definition

A phosphene is a consciously perceived visual experience, typically a localized flash of light, which, rather

than being elicited by a visual stimulus, is induced by non-visual stimulation of nerves within the visual system. Phosphenes may, for example, be produced by pressure in the eyeball inducing neural activity in the retina or by magnetic or electrical stimulation of visual areas in the cerebral cortex.

► [Blindsight](#)

Phosphodiesterase Inhibitors (PDEIs)

Definition

Drugs that inhibit the function of phosphodiesterases (PDEs). These molecules elevate cAMP, resulting in upregulation of PKA and CREB signaling and down-regulation of NF- κ B. Consequently, they are neuroprotective and anti-inflammatory agents.

- [CREB](#)
- [Cyclic AMP](#)
- [Neuroinflammation – PDE Family Inhibitors in the Regulation of Neuroinflammation](#)
- [NF- \$\kappa\$ B](#)

Phosphodiesterase (PDE)

Definition

Denotes a class of enzymes that hydrolyze the cyclic nucleotides cAMP and cGMP (second messengers).

PDEs have an important role as regulators of signal transduction mediated by these second messengers.

There are 11 families of proteins with this enzymatic activity (PDE1-PDE11) and more than 50 isoforms in total.

- [Phosphodiesterase: A family of inhibitors in the regulation of neuroinflammation](#)
- [Neuroinflammation – PDE Family Inhibitors in the Regulation of Neuroinflammation](#)

Phospholipids

Definition

The major lipid molecule of the cell membrane, composed of two fatty acids linked through glycerol phosphate to a polar group.

- [Membrane Components](#)
- [Plasma Membrane - Structure and Functions](#)

Phosphorylation

Definition

A reaction involving the addition of a phosphate group to a molecule. Many enzymes are activated by the covalent bonding of a phosphate group. The oxidative phosphorylation of ADP forms ATP.

- [Energy Sensing and Signal Transduction in Skeletal Muscle](#)

Photocycles

Definition

Cycles, or rhythms, in environmental lighting condition.

As with any rhythm, these can vary with respect to several parameters such as their period, phase and amplitude. Photocycles also vary with respect to the relative duration of their different phases and their waveforms. Some, for example, are sinusoidal and others have abrupt transitions between their light and dark phases. Animals use changing photocycles to anticipate and prepare for daily and seasonal changes in the environment, and their responses to these changes can be influenced by all of the parameters noted above.

Photo-Inactivation Technique

Definition

A technique to selectively lesion individual neurons within the nervous system. Fluorescent dyes are intracellularly injected into cells that die upon illumination by a laser beam or ultraviolet light source. Other nearby neurons are not affected. This technique has been successfully used to isolate putative pacemaker neurons in functional neuronal networks.

- Bursting Pacemakers
- Stomatogastric Ganglion

Photoperiodic Time Measurement

Definition

The measurement by organisms of the duration of the light relative to the dark phase of a light-dark cycle, often abbreviated as PTM. Photoperiodic time measurement enables temperate zone organisms to anticipate and prepare for seasonal changes in their environments.

In vertebrates, the pineal gland plays an important role in the system via its seasonally changing patterns of secretion of the hormone melatonin.

- Photocycle
- Pineal Gland

Photon Catch

Definition

The number of photons absorbed over a given duration by an individual photoreceptor, or class of photoreceptors. The probability of photon absorption depends on photon wavelength, but all subsequent steps of phototransduction are wavelength-independent.

- Photoreceptors
- Phototransduction
- Retinal Color Vision in Primates

Photoperiodism

Definition

The use of daylength by organisms to prepare for seasonal changes in their environments. Animals may use either the rising or the falling phase of the annual rhythm in photoperiod as a signal to anticipate the arrival of spring or the coming of winter conditions, respectively. In mammals, photoperiodism can promote changes in a variety of parameters including, for example, pelage, body weight, reproductive function, activity levels, and aggressive behavior. Some animals use declining photoperiods to prepare for winter conditions and others use the rising phase to prepare for the arrival of spring. In mammals, photoperiodism involves the pineal gland, which signals the changing seasons via its changing pattern of secretion of the hormone melatonin.

- Hibernation
- Seasonality

Photoperiod

Definition

The term “photoperiod” refers to the duration of the light phase of a light-dark cycle. In biology, the term is most commonly used in the context of changes in daylength that many temperate zone organisms use to anticipate and prepare for seasonal changes in their environments.

- Photocycle

Photopic

Definition

Daylight conditions or vision.

Photopigments

NATHAN S. HART

School of Biomedical Sciences, University of Queensland, St. Lucia, Brisbane, QLD, Australia

Synonyms

Visual pigments; Rhodopsins; Porphyropsins; Visual purple

Definition

Photopigments are ►G-protein-coupled transmembrane proteins contained within the ►photoreceptors. Their function is to absorb the incident light and trigger a biochemical cascade that alters the electrical properties of the photoreceptors and, ultimately, modulates the rate of ►glutamate release (see ►Phototransduction).

Characteristics

Description of the Structure

Photopigments are light-sensitive single-chain polypeptides, belonging to the family of ►G-protein-coupled receptors (GPCRs), capable of activating heterotrimeric G-proteins such as *transducin* (see ►Phototransduction). The photopigments of all animals, and even some archaeobacteria, share a common structural conformation that consists of seven α -helical transmembrane segments and an extracellular (or, in the case of vertebrate rod photoreceptors (►Photoreceptors), intradiscal) amino (N) terminus [1]. These similarities reflect the ancient evolutionary origin of photopigment molecules. Photopigments differ from other GPCRs in that light, rather than another molecule, is the ►ligand that stimulates the receptor. This photosensitivity arises from the physical behavior of a ►chromophore molecule embedded in a pocket formed by the protein's transmembrane domain [2].

Opsins

The proteinaceous component of the photopigment is called an ►opsin, and the amino acid sequence of its polypeptide chain determines both its receptor properties and, in combination with the chromophore, its spectral absorbance. Opsins contain 350–500 amino acids, and comparisons of sequence homology reveal that all vertebrate ►visual pigments belong to one of five distinct classes: SWS1, SWS2, RH1, RH2 and M/LWS [3]. Moreover, the gene duplication events that led to the separation of these different opsin classes predate the divergence of the jawed and jawless vertebrate lineages [4].

In functional terms, photopigments are classified by their wavelength of maximum absorbance ($\lambda_{\max}$). In most instances, photopigments belonging to the same opsin gene class have a $\lambda_{\max}$ value in a similar region of the visible spectrum, although there is considerable overlap between classes. SWS1 opsin genes code for ultraviolet- or violet-sensitive cone photopigments with $\lambda_{\max}$ values between 355–440 nm. SWS2 opsin genes produce short-wavelength-sensitive (“blue”) photopigments with $\lambda_{\max}$ values between 410 and 475 nm. RH1 and RH2 opsin genes generate medium-wavelength-sensitive (“green”) photopigments with $\lambda_{\max}$ values between 460–540 nm in rod and cone photoreceptors, respectively. M/LWS opsin genes code for long-wavelength-sensitive (“red”) cone photopigments with $\lambda_{\max}$ values between 505–630 nm.

Birds, turtles and some fish have retained and express all five opsin genes. These species usually possess at least four spectrally distinct cone types and have tetrachromatic color vision (►Color processing). However, throughout vertebrate evolution there has been a tendency for certain taxa to lose opsin classes that were present in their ancestors. For example, some reptiles (e.g. lizards) have lost the RH1 rod opsin as a consequence of the loss of rod photoreceptors from their ►retina. Most placental mammals lack both the SWS2 and RH2 cone opsin genes and are dichromats. Many marine mammals have even lost the SWS1 gene and with it any chance of color vision. However, some primates (including humans) have re-evolved a third cone opsin via a duplication of their M/LWS opsin gene and have trichromatic color vision.

In most species, only one type of opsin is expressed in a given photoreceptor type. However, there are instances where two or more opsins are co-expressed, giving rise to a mixture of photopigments with different $\lambda_{\max}$ values in a single *outer segment* (►Photoreceptors). In mice and rabbits, SWS1 and M/LWS opsins are co-expressed within the same cone photoreceptor and the relative proportion of the two photopigments varies with retinal location. Co-expression of two or more opsins may also occur in some fish while they undergo an ontogenetic shift in habitat light environment.

Chromophores

Vertebrate photopigments employ two different chromophores, 11-*cis* retinal and 11-*cis*-3,4-didehydroretinal, which are the aldehydes of vitamin A₁ and A₂, respectively. Photopigments based on 11-*cis* retinal (►rhodopsins), are generally found in mammals, birds and marine fish. Photopigments based on 11-*cis*-3,4-didehydroretinal (►porphyropsins) are characteristic of freshwater fish and turtles. Different chromophores can

be used interchangeably with the same opsin. However, a porphyropsin photopigment will have a λ_{max} value shifted towards longer wavelengths compared to a rhodopsin photopigment utilizing the same opsin, a phenomenon called the “chromophore shift”.

Many aquatic species, including some lampreys, teleost fish, elasmobranchs and amphibians, are capable of producing both rhodopsin and porphyropsin photopigments. In most cases, the chromophore type changes from 11-*cis* retinal to 11-*cis*-3,4-didehydroretinal in response to an ontogenetic shift in habitat type from fresh to salt water (or vice versa). The long-wavelength spectral shift induced by porphyropsin use is considered to be an adaptation to the relatively red-shifted illumination in most freshwater or estuarine habitats compared to terrestrial or marine light environments. Intriguingly, some terrestrial reptiles, such as the true chameleons (Chamaeleonidae), maintain [▶rhodopsin/▶porphyropsin](#) mixtures of the same opsin type within individual cone photoreceptors, although in the absence of ontogenetic shifts in habitat type the functional significance is unclear.

Spectral Absorbance

The absorbance spectrum of an unbleached photopigment is characterized by four distinct peaks (Fig. 1). The first and most visually relevant of these is the so called α -peak. When classifying the spectral absorbance of photopigments, the λ_{max} value quoted usually refers to the wavelength position of the α -peak, which represents the main absorbance band of the bound chromophore. The α -peak varies in λ_{max} from about 350 to 620 nm, depending on both chromophore type and its physicochemical interactions with the opsin apoprotein

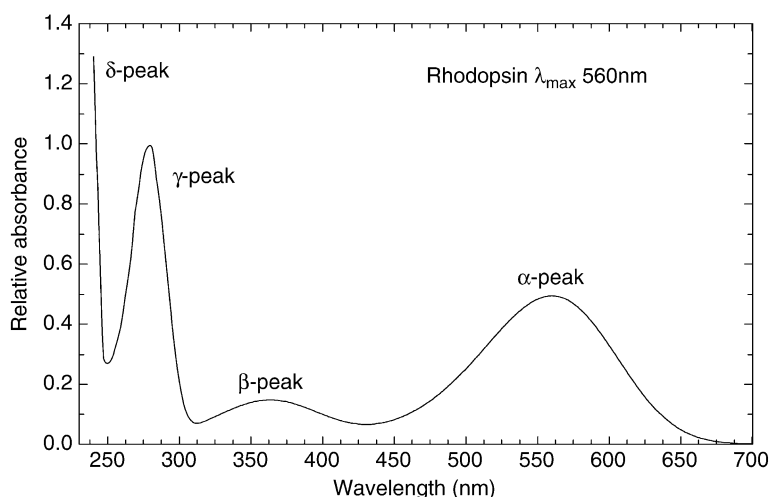
(see section entitled Spectral Tuning and the Opsin Shift). A second, smaller peak (β -peak) occurs at shorter wavelengths and is due to the *cis*-band of the chromophore. The wavelength position of the β -peak is positively correlated to that of the α -peak but varies over a much smaller wavelength range (310–390 nm). The third (γ -peak; 280 nm) and fourth (δ -peak; 231 nm) absorbance peaks are caused by tyrosine and tryptophan residues in the opsin and a variety of organic bonds in the photopigment, respectively [5].

Generally speaking, we are only concerned with the absorbance of the α -peak because wavelengths to which the other absorbance peaks are sensitive are prevented from reaching the photoreceptors by absorption of short wavelengths by the [▶ocular media](#) or other spectral filters in the retina. For example, the human lens and macula contain carotenoid pigments (lutein and zeaxanthin) that prevent light of wavelengths shorter than about 400 nm from reaching the photoreceptors. However, in several other vertebrate (and invertebrate) species, ultraviolet light (UV, 300–400 nm) is allowed to enter the eye to stimulate specialized UV-sensitive photopigments and the β -peak of photopigments with longer λ_{max} values may absorb some of this light.

Regulation of the Structure

Chromophore Photosensitivity and the Schiff's Base Linkage

All opsins contain a lysine residue at a particular site on the interior surface of the chromophore-binding pocket that couples to the chromophore via a Schiff's base bond (aldimine linkage). In vertebrate photopigments, the Schiff's base is usually [▶protonated](#), and its positive charge is balanced by a negatively charged residue



Photopigments. Figure 1 Absorbance spectrum of a rhodopsin (11-*cis* retinal-based) photopigment. See text for details.

(almost invariably glutamate) that acts as a ► **counterion** to stabilize the linkage electrostatically. This charge distribution is fundamental to the photosensitivity and wavelength specificity of the photopigment. When the chromophore absorbs a photon of light, it undergoes a conformational change and flips from the less stable 11-*cis* configuration to the more stable all-*trans* ► **isomer** (see ► **Phototransduction**). This causes a major structural rearrangement that displaces the Schiff's base from its interaction with the glutamate counterion. The subsequent loss of electrostatic stability results in further structural rearrangement of the opsin, deprotonation of the Schiff's base and generation of the active form of the photopigment (metarhodopsin II) [6].

Spectral Tuning and the Opsin Shift

Free chromophore (retinaldehyde) has a peak absorbance at 375 nm. When combined with a simple amino-group ($-NH_2$) containing-compound (n-butylamine), the protonated retinaldehyde-Schiff's base complex formed has a λ_{max} at 440 nm [7]. The difference in λ_{max} between the protonated retinaldehyde-Schiff's base complex and the α -peak of a given opsin-retinaldehyde photopigment is called the "opsin shift."

The magnitude and direction of the opsin shift depend on a variety of molecular interactions, all of which are directly attributable to the amino acid sequence of the opsin. In particular, the interactions of charged, polar or polarisable amino acid residues with the chromophore may affect the strength of the interaction between the protonated Schiff's base and the glutamate counterion, and/or alter the delocalization of charge along the length of the chromophore. A reduction in charge delocalisation along the chromophore, or a strengthening of the Schiff's base-counterion interaction (which helps to prevent charge delocalisation) increases the stability of the chromophore and short-wavelength-shifts the photopigment λ_{max} as a result of the higher energy required for photoisomerization. In contrast, an increase in charge delocalisation, or a weakening of the Schiff's base-counterion interaction, decreases the energy required for photoisomerization and results in a long-wavelength-shifted photopigment [8].

Thus, by altering the types of amino acid present within the opsin polypeptide, at specific locations that are close enough to interact electrostatically with the chromophore, the λ_{max} of a rhodopsin photopigment can be varied almost continuously from 350 to 575 nm (as far as 630 nm in the case of porphyropsin photopigments). In addition to a λ_{max} 500nm RH1 rod photopigment, the human retina contains three cone photopigments with λ_{max} values at 430 (SWS1), 530 and 560 nm (M/LWS). The mechanisms of spectral tuning of vertebrate (especially mammalian) M/LWS

photopigments are probably the best understood of all opsin genes and, in most species, their λ_{max} values are determined by various combinations of amino acid substitutions at just five locations in the opsin apoprotein, the so called "five sites rule" [3].

Anion Sensitivity and Spectral Tuning

In addition, most vertebrate M/LWS photopigments are thought to be spectrally tuned in part by the binding of anions, more specifically chloride ions, at locations on the opsin close to the Schiff's base linkage. For example, chicken M/LWS photopigment has a native λ_{max} value of 565 nm that can shift to 520 nm in the absence of chloride ions. It is thought that the Schiff's base counterion is complex, and the inclusion of an exchangeable chloride ion helps to maintain a relatively delocalized distribution of charge on the chromophore and, consequently, red shifts the λ_{max} of the photopigment [9].

Function

Photopigments absorb photons of light and trigger the enzymatic activity of the photoreceptor G-protein transducin. This leads to a biochemical cascade that ultimately results in a change in the rate of release of ► **neurotransmitter** by the photoreceptor and a detectable neural signal. Although the primary function of a photopigment is to detect light of any wavelength, the divergence of the ancestral photopigment gene into multiple spectral types very early in evolution suggests that there is considerable selection pressure on the spectral tuning of photopigments. Although generalisations are difficult to make, the number of different photopigment types and their λ_{max} values are almost certainly determined by the spectral distribution of the available light, the need to find food and potential mates, and avoid predators.

Pathology

► **Retinitis pigmentosa (RP)** (► **Inherited retinal degenerations**) is a collection of genetically inherited diseases that result in the degeneration of photoreceptors and the retinal pigment epithelium. Symptoms include night blindness and the loss of peripheral vision. Over 100 different point (single amino acid) mutations in the gene encoding rod opsin, located on autosomal chromosome 8, are known to cause RP, possibly as a result of the failure of the mutant opsin to fold correctly, bind retinal or activate transducin [6].

The genes coding for green- and red-sensitive cone pigments (M/LWS opsins) in humans are carried on the X chromosome. Mutations in these genes are responsible for the different forms of red-green ► **color blindness** and, because of their location on the X chromosome, are more apparent in males, which have only one copy of the gene.

These include amino acid substitutions that alter the $\lambda_{\max}$ of the green- (deuteranomaly) or red-sensitive (protanomaly) photopigments and result in anomalous color vision, or cause the complete loss of green- (deuteranopia) or red-sensitive (protanopia) cones [10].

The SWS1 gene encoding the human blue-sensitive cone opsin is located on chromosome 7. Mutations in the SWS1 gene that cause a spectral shift in the expressed pigment (tritanomaly) or a loss of functional blue cones (tritanopia) result in blue-yellow color blindness. As the SWS1 gene is carried on a pair of autosomal chromosomes, mutations in both copies are required to produce tritanopia. Consequently, blue-yellow color blindness occurs less frequently than red-green color blindness.

References

1. Stenkamp RE, Filipek S, Driessen CA, Teller DC, Palczewski K (2002) Crystal structure of rhodopsin: a template for cone visual pigments and other G protein-coupled receptors. *Biochimica Biophys Acta* 1565:168–182
2. Sakmar TP, Menon ST, Marin EP, Awad ES (2002) Rhodopsin: insights from recent structural studies. *Annu Rev Biophys Biomol Struct* 31:443–484
3. Yokoyama S (2000) Molecular evolution of vertebrate visual pigments. *Prog Retin Eye Res* 19:385–419
4. Collin SP, Knight MA, Davies WL, Potter IC, Hunt DM, Trezise AE (2003) Ancient colour vision: multiple opsin genes in the ancestral vertebrates. *Curr Biol* 13: R864–R865
5. Rodieck RW (1973) The vertebrate retina. WH Freeman and Company, San Francisco
6. Pepe IM (2001) Recent advances in our understanding of rhodopsin and phototransduction. *Prog Retin Eye Res* 20:733–759
7. Nakanishi K (1991) 11-cis-retinal, a molecule uniquely suited for vision. *Pure Appl Chem* 63:161–170
8. Hunt DM, Wilkie SE, Bowmaker JK, Poopalasundaram S (2001) Vision in the ultraviolet. *Cell Mol Life Sci* 58:1583–1598
9. Kleinschmidt J, Hárosi FI (1992) Anion sensitivity and spectral tuning of cone visual pigments *in situ*. *Proc Natl Acad Sci USA* 89:9181–9185
10. Rodieck RW (1998) The first steps in seeing. Sinauer Associates, Sunderland, MA

Photoreception

Definition

The sensory process by which light energy is converted into a biologically relevant signal.

Photoreceptor, Variety and Occurrence

MEGUMI HATORI, SATCHIDANANDA PANDA
The Salk Institute for Biological Studies, La Jolla, CA, USA

Definition

Photoreceptors regulate light-dependent physiologies; image formation and non-image forming adaptation such as regulation of circadian entrainment, seasonal reproduction and body color change. The vertebrate retina contains three types of photoreceptors: rods, cones and ipRGCs. In non-mammalian vertebrates, the pineal complex, deep brain, skin, parapineal and parietal eye are also known to contain photoreceptors. Each vertebrate photoreceptor contains a photopigment consisting of a protein called opsin and vitamin-A-based light-absorbing molecule (chromophore), 11-*cis* retinal.

Characteristics

Introduction

Dynamic adaptation to ambient light is central to survival of most animals. Light adaptation is achieved by two basic mechanisms: image formation for rapid adaptation to the physical environment and non-image forming adaptation of physiology and behavior to ambient light quality. The image-forming function is exclusively mediated by the eye – a specialized optical structure with a lens that projects an image to the ►retina. ►Cone and ►rod photoreceptors of the retina capture the image and send the information to the visual cortex for image reconstruction [1]. The non-image forming (NIF) photoresponses vary widely, from rapid adjustment of pupil diameter to progressively slow responses, such as skin color adaptation in amphibians, adaptation of the circadian clock to the daily day–night cycle, and seasonal reproductive behavior. Accordingly, the underlying ►photopigments vary widely in (i) the cell types of expression, (ii) anatomical location and (iii) target cells or effector process.

The photopigment for most of the above responses comprises an opsin family of G-protein coupled receptor and a light-sensitive vitamin-A based chromophore. The amino acid sequence of the opsin scaffold determines (i) the spectral properties, (ii) specificity of the downstream signaling pathway and (iii) interaction with other regulatory molecules. Although flavin-based photopigments, such as ►cryptochromes, have been implicated in the circadian photoresponses of insects, no such light-dependent function of cryptochrome molecules in vertebrates has been conclusively established.

In mammalian vertebrates all of the photoresponses originate from photopigments of the retina. In non-mammalian vertebrates, however, additional anatomical

structures such as the parietal eye, ►**pineal**-, parapineal-complex, deep brain, and skin are also known to contain functional photoreceptors which primarily mediate NIF photoresponses.

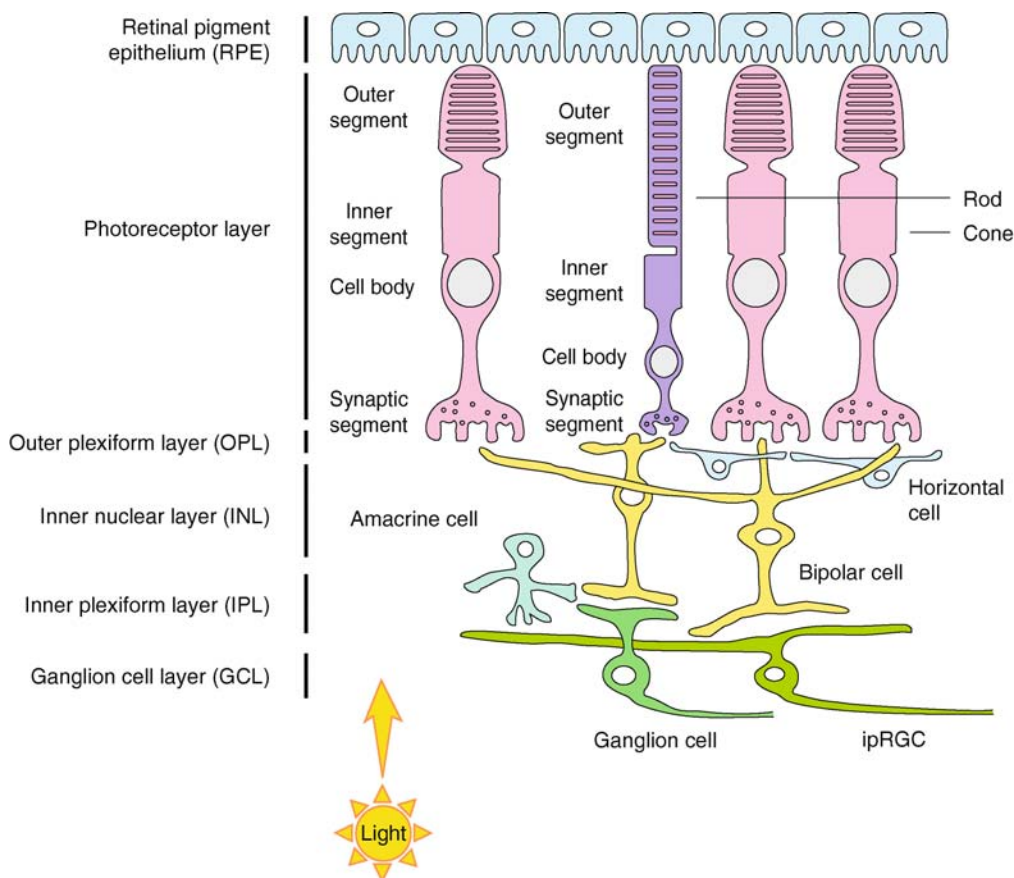
Ocular Photoreceptors in the Vertebrates

The rod and cone cells are the predominant photoreceptors of the retina. They exhibit exquisite subcellular specialization such that the different cellular functions are stratified along the length of the cells. The nuclei mark a virtual functional boundary, with the distal segment functioning in photoreception, while the segment proximal to the lens makes synaptic connections to other cell types of the retina. The photopigment in these cells is tightly packed into specialized membranes that are organized into rod or cone like structures in the outer segment of rod or cone cells, respectively (Fig. 1).

The outer segment is connected to the rest of the cells by a narrow structure, the ciliary stalk. Between the ciliary stalk and the nuclei, various organelles such as

mitochondria, the Golgi apparatus and the endoplasmic reticulum are concentrated in stratified layers. The inner segment of the rod/cone cells contain the synaptic structures for signal transduction to other cell types of the retina, which ultimately connect to the ►**retinal ganglion cells** (RGCs) – the only retinal cell type that makes synaptic connections to the brain. No other cell types of the mammalian vertebrate retina were known to be directly light sensitive until the discovery of ►**intrinsically photosensitive RGCs** (see section ►**ipRGCs**).

In non-mammalian vertebrates, however, opsin photopigments are expressed in additional retina cell types. The horizontal and amacrine cells in the retina of teleost fish express vertebrate ancient (VA)-opsin. In birds and amphibians melanopsin mRNA is extensively expressed in both inner and outer nuclear layers of the retina. However, in all animals the rod and cone cells are the most characterized photoreceptors of the retina.



Photoreceptor, Variety and Occurrence. Figure 1 Schematic structure of the vertebrate retina. Vertebrate retina is composed of multiple cell layers with specialized functions. The rods and cones of the outer nuclear layer and a few RGCs of the ganglion cell layers are bona fide photoreceptors or intrinsically photosensitive. Other cell types such as horizontal, bipolar, amacrine and ganglion cells participate in light signal processing and signal transduction to the brain.

Rods

Typically, a rod cell is sensitive enough to respond to a single photon of light and therefore is responsible for scotopic or dim-light vision in night (Table 1) [1,2]. With increasing light intensity at dawn, the rods become saturated or “bleached”, thus under daylight the less sensitive cones mediate visual function. Rods respond slowly to light and have longer integration time than cones do.

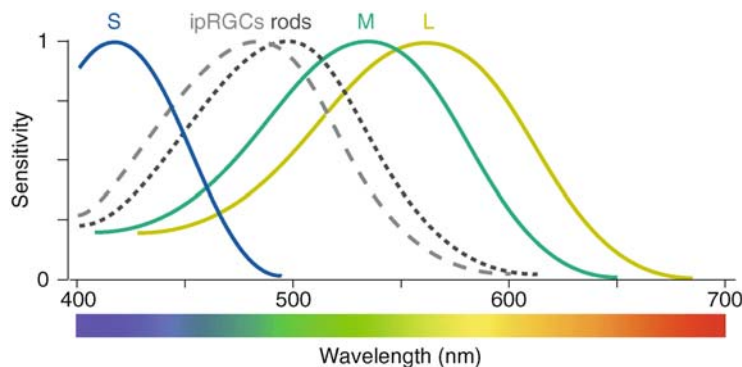
Generally, each rod or cone cell expresses only one type of opsin photopigment, thus the photoresponses of the cell reflect that of the photopigment. Most vertebrate

retina contain a single type of rod expressing rhodopsin with peak sensitivity ~ 500 nm (Fig. 2), although several amphibians like toads and salamanders are known to have two types of rods, called the red-rods and the green-rods, which have distinct absorbance spectra.

The photopigment in rod cells is densely packed into specialized disc membranes that are stacked to form the rod outer segment. The outer segment of both rods and cones are continuously renewed. In rods, new rhodopsin molecules are synthesized just before dawn and the distal discs are shed and phagocytosed by the retinal pigment epithelium (RPE) cells in the morning.

Photoreceptor, Variety and Occurence. Table 1 Comparison of rods, cones and ipRGCs. Modified from [3]

	Rods	Cones	ipRGCs
Major function	Scotopic/night vision	Photopic/daytime vision	Non-image forming photoresponses
Location	Outer nuclear layer	Outer nuclear layer	Ganglion cell layer
Photopigment	Rod opsin (rhodopsin)	Cone opsins	Melanopsin
Localization of opsins	Outer segment	Outer segment	Soma, dendrites, and axon.
Sensitivity	High	Moderate (less sensitive than rods)	Low
Integration time	Longer integration time than cones (tens of milliseconds)	Respond faster than rods	Seconds
Light response of membrane potential	Fast hyperpolarizing	Fast hyperpolarizing	Slow depolarizing
Action potentials	No	No	Yes
Role of RPE for photopigment regeneration	Essential	Essential	Apparently unnecessary
Receptive field	Very small	Very small	Very large (tens of microns)
Number of cells in human eye	~ 120 million	~ 6 million	$<5,000$
Spatial distribution in human eye	Peripheral	Fovea	Uniform



Photoreceptor, Variety and Occurence. Figure 2 Spectral sensitivity of mammalian ocular photoreceptors. Spectral sensitivities of cones (S-cones, M-cones and L-cones), rods and ipRGCs.

Such temporal regeneration of rods coincides with their primary role in scotopic vision.

Cones

Cones are cone-shaped photoreceptors in the retina that can function under bright light and are responsible for photopic or bright-light vision (Table 1) [1,2]. Cones are less sensitive to light intensity than the rods. On the other hand, response times to stimuli are faster than those of rods, and they are also able to perceive color, finer detail and more rapid changes in images. Unlike the disc membranes of the rod, the outer segment of the cones is formed by invagination of the plasma membranes. The photopigments of the cones are primarily synthesized prior to dusk, and membranes from the tips of the cones are shed in the evening. Based on peak spectral sensitivity, most animals contain two types of cones, one at >500 nm (long wavelength cone or L-cone) and one at <500 nm (short wavelength cone or S-Cone). Some animals including teleost fish, Old World monkeys and humans have one additional cone-type absorbing in the medium wave (M-cone). There are several exceptions; for example, several nocturnal mammals like owl monkeys, a New World monkey, have only one type of cone. Sensitivities of human S-cones, M-cones and L-cones are to ~420 nm (blue), ~530 nm (green) and ~560 nm (yellowish-green) wavelengths, respectively (Fig. 2). S-cones are smaller in number than M- and L-cones and are sparse in the fovea region. The difference in the signals received from the three cone types allows the brain to distinguish millions of colors. As cones are functional under bright light, they require rapid regeneration of the *all-trans* retinal. There is some evidence that unlike the rods which depend on the RPE cells, the cones depend on a different type of retinal cycle involving cones and the Müller cells of the retina.

ipRGCs (Intrinsically Photosensitive Retinal Ganglion Cells)

The ipRGCs are intrinsically photosensitive and constitute only 1–2% of the retinal ganglion cells of the adult mammalian retina. They do not play any major role in image-forming vision but are important photoreceptors for NIF photoresponses, which include light entrainment of the master circadian oscillator resident in the hypothalamic **suprachiasmatic nucleus (SCN)**, light suppression of pineal melatonin synthesis and release, light modulation of activity and pupillary light reflex (Table 1) [3,4].

These adaptive photoresponses are almost intact in several animal models with complete rod/cone degeneration and exhibit an action spectrum characteristic of the absorption spectrum of the opsin class of photopigments with a peak around 480 nm. **Melanopsin**, a novel photopigment expressed in these cells, mediates

photosensitivity (Fig. 2). Unlike the rod/cone photoreceptors, ipRGCs exhibit no polarized expression of the photopigment; melanopsin immunoreactivity is localized to membranes of the dendrites, somas and possibly axons of these cells. Cell bodies of the ipRGCs are mostly resident in the RGC sublayer, while the dendrites heavily arborize within the inner plexiform layer spreading to as many as tens-of-microns in diameter of receptive fields (Fig. 1). The dendrites make synaptic contacts with both rod and cone bipolar cells and receive rod/cone inputs, and hence are unique photoreceptor cells of the retina with two almost independent major functions: (i) to initiate photochemical reaction by melanopsin as well as (ii) to transmit rod/cone initiated photoresponse. Unlike other RGCs, axons of these ipRGCs primarily project to the SCN, where they are almost equally distributed between contra- and ipsi-lateral SCN. They also send additional projections to other brain regions implicated in NIF photoresponses.

Isolated ipRGCs depolarize in response to light and generate action potentials in a melanopsin-dependent manner. They exhibit long latency of light response and are depolarized as long as the lights are on and have long deactivation kinetics. The native molecules and channels underlying the photoresponses of the ipRGCs have not conclusively been established. However, the persistence of the non-image forming adaptive photoresponses in animal models deficient in several signaling components and channels mediating rod/cone photoresponses imply the ipRGCs recruit a distinct set of signaling molecules.

Phototransduction Mechanism

In all opsin-based photopigments, the first step in photoresponse begins with the photoisomerization of a vitamin-A based *cis*-isomer of retinal to its *trans*-isomer. The resultant conformational change of the protein triggers activation and release of a Gai/Gao (most vertebrate opsins) or Gaq/Ga11 (melanopsin) class of G-protein. The Gai/Gao class of effector G-protein of rod/cones, also known as transducin (Gt), activates a phosphodiesterase, which in turn rapidly degrades cGMP and causes closing of the cyclic nucleotide gated channels. Hence, photoactivation of rod/cone photoreceptors leads to membrane hyperpolarization and a pause in neurotransmitter glutamate release. On the other hand, it is presumed that photoactivated melanopsin activates the Gaq/Ga11 class of G-proteins, which in turn activates phospholipase C (PLC). Activated PLC can signal through several mechanisms, including intracellular calcium release, increase in IP₃ and DAG, and ultimately opening of a channel leading to membrane depolarization, and release of neurotransmitters, such as glutamate and adenylylate cyclase-activating peptide 1. Signal

termination occurs at various steps including receptor, G-protein and downstream components. Finally, regeneration of active photopigment occurs, enabling another round of photoresponses to be initiated. The all-*trans* retinal from rod/cone cells is transported to the RPE cells where an elaborate multistep enzymatic process ensures sufficient retinal regeneration for use by the rod/cone photoreceptors. Melanopsin, on the other hand is presumed to isomerize the resultant all-*trans* retinal to the active 11-*cis* isomer by an intrinsic photoisomerase activity.

Extraocular Photoreceptors in Nonmammalian Vertebrates

While mammals use ocular photopigments for all types of photoresponses, several non-mammalian vertebrates express functional photopigments outside their eyes, including the parietal eyes, pineal, parapineal glands, dermal cells, and in brain. Organisms use them primarily for physiological adaptation to the ambient light quality. Some of these tissues such as pineal and parietal eyes develop embryologically from the diencephalons, which also gives rise to the eye. Accordingly the photoreceptor cells of these organs show some morphological similarities with those of the retina, and they also express multiple photopigments in distinct or in the same cell types.

Pineal Photoreceptor

In lower vertebrates such as lampreys, fishes, amphibians, lizards and birds, the pinealocytes have both intrinsic photosensitivity as well as neuroendocrine function, such that under cultured conditions of isolated pineal gland, they are light-sensitive and have the ability to produce ►melatonin in a circadian and light-dependent manners.

The action spectrum of the photosensitivity of the isolated chicken pineal resembles the absorption spectrum of rhodopsin. Consistent with this prediction, an opsin-like protein was identified in the chicken pineal gland and named pinopsin (=pineal opsin), the first functional opsin to be discovered outside the retina [5]. Pinopsin upon reconstitution with 11-*cis* retinal forms a functional photopigment with peak sensitivity at 468 nm and can couple to Gt. Besides pinopsin, a chicken red-sensitive cone pigment, called iodopsin, and melanopsin are also expressed in the chicken pineal gland. Pinopsin is not detected in fish and mammals. Alternatively, the pineal gland of zebrafish expresses exo-rhodopsin (=extra-ocular ►rhodopsin). Exo-rhodopsin is expressed in the majority of pineal cells, but not in retinal cells. The pineal photopigments might function to modulate melatonin secretion in a cell autonomous manner. Additionally, they also make synaptic connections with neurons that project to various thalamic and hypothalamic regions. Mammals have lost the intrinsic photosensitivity of pinealocytes, but they still retain circadian regulation of

melatonin secretion, which is also light regulated by ocular photopigments via a multisynaptic pathway.

Parietal Eye Photoreceptors

Several lizards harbor an extra eye-like structure called the parietal eye that does not appear to have any role in image-forming vision, but rather helps adapt to light quality. Like the eye, the parietal eyes also contain various cell types stratified into distinct layers. However, unlike the image-forming photoreceptors, which hyperpolarize in response to light, the parietal eye photoreceptors either depolarize or hyperpolarize in response to specific wavelengths of light. These photoreceptor cells express two different types of opsins – pinopsin and parietopsin in the same cell type [6]. Distinct absorption spectra of these two opsins and functional coupling to distinct signaling mechanisms may produce such unique membrane potential properties of the parietal eye photoreceptor cells.

Photoreceptors in the Deep Brain

Most photoreceptor cells described above are located outside or immediately beneath the skull. However, in some vertebrates there is evidence for photoreceptors in the deep brain which largely mediate long term seasonal photo-adaptations. The photoperiodic change in gonad function persists in pinealectomized and enucleated Japanese quails and exhibits peak sensitivity around 500 nm. Actually, ~500 nm wave-length light can transmit through the scalp and skull and reach to the deep brain.

Several opsins of the eye and pineal glands are shown to be expressed in deep brain, but their functions are still almost unknown. Rhodopsin was cloned from lateral septum of pigeons, pinopsin-expressing cells exist in the anterior preoptic nucleus of toads, VAL (vertebrate ancient-long) opsin is localized in a small portion of cells surrounding the diencephalic ventricle of central thalamus in zebrafish, and melanopsin is expressed in hypothalamic sites of *Xenopus laevis*.

References

1. Rodieck RW (1998) The first steps in seeing. Sinauer Associates, Sunderland, MA
2. Solomon SG, Lennie P (2007) The machinery of color vision. Nat Rev Neurosci 8:276–286
3. Berson DM (2003) Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci 26:314–320
4. Nayak SK, Jegla T, Panda S (2007) Role of a novel photopigment, melanopsin, in behavioral adaptation to light. Cell Mol Life Sci 64:144–154
5. Okano T, Yoshizawa T, Fukada Y (1994) Pinopsin is a chicken pineal photoreceptive molecule. Nature 372:94–97
6. Su CY, Luo DG, Terakita A, Shichida Y, Liao HW, Kazmi MA, Sakmar TP, Yau KW (2006) Parietal-eye phototransduction components and their potential evolutionary implications. Science 311:1617–1621

Phototransduction

NATHAN S. HART

School of Biomedical Sciences, University of Queensland, St. Lucia, Brisbane, QLD, Australia

Synonyms

Visual transduction cascade

Definition

Phototransduction is the process by which light energy that is absorbed by ►photopigments contained within ►retinal photoreceptors (►Photoreceptors) is converted into a biochemical signal that leads to a ►hyperpolarization of the photoreceptors.

Characteristics

Description of the Process

Photoisomerization

Phototransduction begins when a photon of light is absorbed by a photopigment molecule. The energy imparted by the photon induces a conformational change in the ►chromophore (see ►Photopigments), in the case of 11-*cis* retinal causing it to flip to the all-*trans* isomer. This transition is called ►photoisomerization, and is the only light-dependent step in the phototransduction process; it is also extremely rapid, taking less than 200 fs [1]. Photoreceptor ►outer segments are densely packed with photopigment molecules to capture as much of the incident light as possible. Nevertheless, only two out of every three photons absorbed by the photopigment succeed in isomerising the chromophore; photopigments have a ►quantum efficiency of about 0.67, regardless of photon wavelength [2]. Energy from photons that are absorbed but do not induce chromophore isomerization is dissipated as heat.

The probability that a photon of light will be absorbed by a photopigment of given spectral sensitivity is dependent on the photon's wavelength. However, an individual photoreceptor is incapable of discriminating between photoisomerization events caused by photons of different wavelength and can only signal the rate of photon capture, a concept known as the "principle of univariance." Wavelength discrimination requires photoreceptors with differing photopigment spectral sensitivities and the ancillary neural mechanisms to compare their output signals, i.e. color vision (►Color processing).

Photopigment Activation

The change in chromophore conformation during photoisomerization alters the local structure of the chromophore-binding pocket of the photopigment

apoprotein (►opsin). These structural rearrangements propagate throughout the tertiary structure of the photopigment, which progresses step-wise through a series of physically and spectroscopically distinct photobleaching intermediates until, through deprotonation of the Schiff's base linkage that binds the chromophore to the opsin, the biochemically active form of the photopigment (R^*) is created [3]. In the case of ►rhodopsin (11-*cis* retinal based) photopigments, the activated form of the molecule is called metarhodopsin II and appears approximately 2 ms after photoisomerization [4].

Transducin Activation

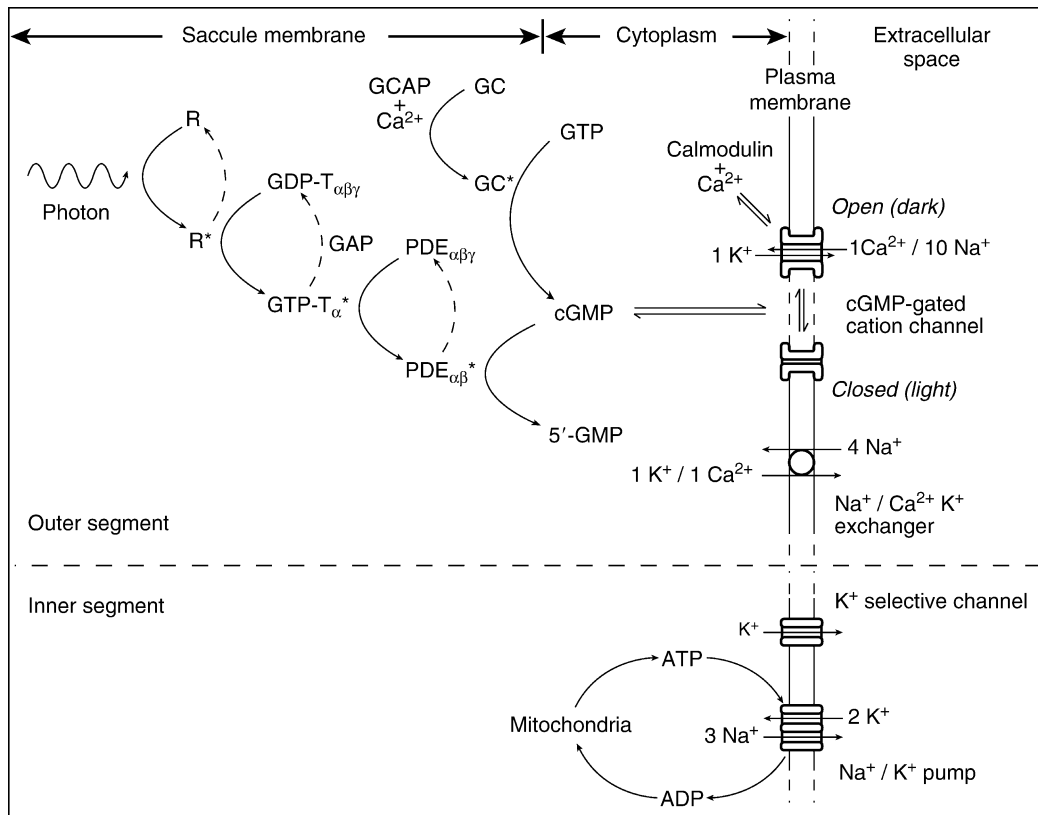
The next stage in the phototransduction process occurs when R^* triggers a biochemical cascade that amplifies the visual signal to a detectable threshold in a stereotyped fashion (Fig. 1). As each R^* is free to diffuse rapidly within the plane of the outer segment disk membrane, and does so randomly as a result of ►Brownian motion, it encounters and activates several hundred ►transducin molecules within about 100 ms [5]. Transducin is a membrane-bound heterotrimeric G protein that consists of three subunits, T_α , T_β and T_γ . Rods and cones contain different isoforms of the three subunits, but the proteins perform the same function in the cascade [6].

Amino acids on the cytoplasmic loops of R^* bind briefly (<0.1 ms) to ►epitopes on the transducin complex, and induce a conformational change in the structure of the T_α subunit that results in the release of a molecule of bound guanosine diphosphate (GDP). When the GDP released from the T_α nucleotide-binding pocket is subsequently replaced with a molecule of guanosine triphosphate (GTP), a further conformational change activates the transducin complex, causing both the detachment of R^* and the dissociation of T_α -GTP from the heterotrimer [1]. At this stage, R^* is then free to move away and activate other transducin molecules before it is eventually deactivated through phosphorylation and binding to ►arrestin (see below).

Phosphodiesterase Activation

Activated GTP-bound transducin T_α subunits have a high affinity for guanosine 3', 5' cyclic monophosphate (cGMP)-specific phosphodiesterase (PDE). PDE is a membrane-bound protein consisting of two catalytic subunits (PDE_α and PDE_β) and two identical inhibitory subunits (PDE_γ). In the dark-adapted state, the catalytic activity of the PDE_α and PDE_β subunits is blocked by their respective PDE_γ subunits [7]. Following illumination and activation of transducin, T_α -GTP binds to PDE and displaces either or both of the PDE_γ subunits, thereby exposing its catalytic sites.

In this second stage of signal amplification, activated PDE_α and PDE_β subunits catalyze the conversion of



Phototransduction. Figure 1 Simplified schematic diagram of the phototransduction cascade in a mammalian rod. Relevant membrane channels are also depicted. Abbreviations: *R*, rhodopsin; *GDP*, guanosine diphosphate; *GTP*, guanosine triphosphate; *T*, transducin; *PDE*, phosphodiesterase; *cGMP*, cyclic guanosine monophosphate; *GMP*, guanosine monophosphate; *GAP*, GTP-ase activating proteins; *GC*, guanylate cyclase, *GCAP*, guanylate cyclase activating proteins; *ATP*, adenosine triphosphate; *ADP*, adenosine diphosphate. An asterisk signifies the activated form of the enzyme. Subscripts indicate the enzymatic subunit(s) present. Dashed arrows represent regeneration steps.

many molecules of cytoplasmic cGMP to 5' guanosine monophosphate (GMP) and rapidly reduce the concentration of cGMP molecules present in the outer segment. cGMP is a **second messenger** in the phototransduction process, and the fall in its concentration is detected by cGMP-gated cation channels in the outer segment plasma membrane, which close. The closure of ionic channels reduces the influx of Na^+ and Ca^{2+} ions and, because K^+ ions continue to be removed from the cell via K^+ -selective channels in the **inner segment**, causes a local hyperpolarization of the photoreceptor's transmembrane potential [4].

Photoreceptor Dark Current, Photocurrents and Hyperpolarization

Phototransduction works by changing the electrical potential across the photoreceptor plasma membrane. Like all living cells, the interior of a photoreceptor is charged negatively with respect to the extracellular space (**Membrane potential – basics**); the resting transmembrane potential of a rod is about -37 mV,

whereas that of a cone is around -46 mV [8]. In the dark, this transmembrane potential is maintained by a balanced flow of cations (predominantly Na^+) into and out of the photoreceptor, known as the dark current (**Photoreceptor dark current**), which has a magnitude of up to -34 pA in rods and -30 pA in cones. In the outer segment, voltage-insensitive cGMP-gated ionic channels allow the entry of ten Na^+ and one Ca^{2+} for every K^+ they expel, and $\text{Na}^+/\text{Ca}^{2+}\text{K}^+$ exchangers (**Ion transporters**) expel one Ca^{2+} and one K^+ while allowing four Na^+ to enter. The influx of 14 Na^+ to the outer segment is balanced by the activity of ATP-driven Na^+/K^+ pumps (Ion transporters) in the inner segment, which admit 2 K^+ for every 3 Na^+ they expel. Several cycles of the Na^+/K^+ pump are required, and the additional K^+ that enter the cell reciprocally pass out of the cell down their concentration gradient via K^+ -selective channels [1,4].

Each cGMP-gated cation channel consists of four subunits, and each subunit is capable of binding one molecule of cGMP at an intracellular domain close to

the C terminus of the polypeptide chain. The channel pore only allows the influx of cations when at least three molecules of cGMP are bound and, to a first approximation, the number of open channels varies as the cube of cytoplasmic cGMP concentration [4]. When the concentration of cGMP falls as a result of light-induced PDE catalytic activity, the number of open channels falls dramatically and the influx of cations to the outer segment is restricted. However, because Na^+ and K^+ ions are still pumped out of the inner segment there is a net loss of positive charge within the photoreceptor. The change in cation flow induced by the absorption of photons is called the **▶photocurrent**. In the case of rod photoreceptors, a single photoisomerization event can hyperpolarize the transmembrane potential with a photovoltage of 1.2 mV [8].

Synaptic Deactivation

Initially, the transmembrane hyperpolarization induced by cGMP-gated cation channel closure is localized to the cytoplasm, near the activated segment of disk membrane (rods) or plasma membrane infolding (cones). However, this charge displacement is gradually redistributed along the entire surface area of the plasma membrane, and the hyperpolarization spreads electronically (**▶Electrotonic spread**) to the inner segment and **▶synaptic terminal**.

The effect of hyperpolarization on the synaptic terminal is to close inward voltage-gated Ca^{2+} channels (**▶Calcium channels – an overview**) in the plasma membrane. However, free Ca^{2+} ions continue to be extruded from the cell by $\text{Na}^+/\text{Ca}^{2+}\text{K}^+$ exchangers, and so the concentration of Ca^{2+} in the synaptic terminal falls [1]. As the rate of **▶synaptic vesicle** fusion with the presynaptic membrane is proportional to the concentration of cytoplasmic Ca^{2+} , the hyperpolarization-induced closure of voltage-gated Ca^{2+} channels results in a graded reduction in the rate of **▶glutamate** release into the synapse.

Regulation of the Process

Deactivation of R^* and the Phototransduction Cascade

During its random diffusion across the membrane surface, R^* inevitably encounters and binds to a molecule of **▶rhodopsin kinase**, which rapidly phosphorylates serine and threonine residues on the photopigment C-terminus [6]. Phosphorylation of R^* dramatically increases its affinity for another cytoplasmic protein, arrestin, which replaces the kinase and deactivates R^* . Arrestin remains bound to the deactivated photopigment until the chromophore is reduced to all-*trans* retinol by retinal dehydrogenase, and dissociates from the opsin protein, approximately 1 s after photoisomerization.

The other components of the biochemical cascade must also be deactivated to ensure a reliable stereotyped response to each photoisomerization event and allow

recovery of the photoreceptor. Once T_α -GTP has bound to and activated PDE, the complex is recognized by other membrane proteins, known as **▶GTPase activating proteins (GAPs)**. Assisted by the inhibitory γ -subunit of PDE, GAP stimulates the intrinsic GTPase activity of T_α , which hydrolyses the bound nucleotide to GDP [9]. Phosphorylated T_α -GDP subsequently detaches from the PDE_γ subunit, thereby inactivating the catalytic activity of PDE, and reassociates with the $T_{\beta,\gamma}$ dimer.

Recovery and Light Adaptation

The fall in concentration of cytoplasmic Ca^{2+} associated with cGMP-gated cation channel closure and transmembrane hyperpolarization provides a mechanism for negative feedback, which controls both the recovery of the photoreceptor and its response to increasing levels of illumination. Decreasing Ca^{2+} levels stimulate, indirectly, the activity of a guanylate cyclase (GC) enzyme that synthesizes cGMP from GTP. GC is activated by guanylate cyclase activating proteins, or GCAPs, that are also Ca^{2+} -binding proteins [6]. The GCAPs in question are unable to activate GC when Ca^{2+} ions occupy two of their specific Ca^{2+} -binding sites. However, when the Ca^{2+} concentration drops, some of the GCAPs are disinhibited and stimulate GC to increase the rate of conversion of GTP to cGMP by a factor of 5–10 [4]. The subsequent increase in cGMP production counteracts the decrease caused by PDE activity and allows some of the cGMP-gated cation channels to reopen, thereby helping to restore the dark current.

Additionally, Ca^{2+} levels modulate the behavior of the cGMP-gated cation channels through the actions of another Ca^{2+} -binding protein, **▶calmodulin**. Calmodulin is a small (17 kD) protein that becomes activated when at least three of its four Ca^{2+} -binding sites are occupied by Ca^{2+} ions. The tetrameric cGMP-gated channel protein consists of two types of subunits, α and β . The β -subunit is larger (155 kD) than the α -subunit (80 kD), and has a calmodulin binding domain on an intracellular portion of the polypeptide chain near the N-terminus [4]. Activated calmodulin can bind to the β -subunit and reduce the affinity of the channel proteins for cGMP, leading to fewer open channels. However, when the cytoplasmic Ca^{2+} concentration is reduced during phototransduction, the subsequent decrease in activated calmodulin levels results in an increased affinity of the channel proteins for cGMP [5]. This leads to a greater number of bound cGMP molecules and the opening of more cation channels.

Both of these Ca^{2+} -modulated negative feedback mechanisms subserve recovery, and potentially **▶light adaptation**, by preventing saturation of the light response, and allow the photoreceptors to respond to incremental changes in light intensity over a wide range of background illumination levels [10]. The importance of these feedback mechanisms is evident

if one considers the responses of photoreceptors to dim flashes of light. At very low light levels, the magnitude of the photocurrent scales linearly with light intensity. If the dark current of a rod is -34 pA and each photoisomerization event causes a photocurrent of 0.7 pA, the rod response would saturate with a flash intensity that caused less than 50 photoisomerizations. However, at higher flash intensities, typically those generating photocurrents of more than one third of the maximal dark current, the increase in photocurrent with increasing light intensity becomes increasingly smaller in an exponential fashion. In this way, rods are able to signal incremental changes in brightness, up to flash intensities that cause around 400–500 photoisomerizations before saturating [4].

Function

Light is a visible form of electromagnetic radiation and, as such, exhibits both wave and particle properties. One property of the particle nature of light is that light energy travels in discrete packets (quanta) called photons. This has two important consequences for vision. Firstly, the visual system must detect quantal events that involve the transfer of miniscule amounts of energy. Secondly, the arrival of photons at the retina is a stochastic Poisson process. Photoreceptor neurons are exquisitely sensitive and can respond to the absorption of a single photon by a photopigment molecule. Phototransduction is the process by which this singular event is sufficiently amplified to create an electrical signal that can reliably be detected by the rest of the visual system.

Pathology

A number of inherited diseases affecting the mammalian retina are caused by mutations in genes that encode components of the phototransduction cascade [1].
 ▶ **Retinitis pigmentosa** (▶ **Inherited retinal degenerations**) – a general term for a number of inherited conditions that cause degeneration of the photoreceptors and retinal pigmented epithelium – can result from mutations in both guanylate cyclase and PDE. In addition, various forms of ▶ **night blindness** are caused by mutations in either the α -subunit of transducin, which reduce the endogenous GTPase activity that mediates PDE inactivation (autosomal dominant night blindness), or in arrestin or rhodopsin kinase (▶ **Oguchi disease**).

▶ Evolution of Eyes

References

1. Pepe IM (2001) Recent advances in our understanding of rhodopsin and phototransduction. *Prog Retin Eye Res* 20:733–759
2. Rodieck RW (1973) *The vertebrate retina*. WH Freeman, San Francisco

3. Sakmar TP, Menon ST, Marin EP, Awad ES (2002) Rhodopsin: insights from recent structural studies. *Annu Rev Biophys Biomol Struct* 31:443–484
4. Rodieck RW (1998) *The first steps in seeing*. Sinauer Associates, Sunderland, MA
5. McNaughton PA (1995) Rods, cones and calcium. *Cell Calcium* 18:275–284
6. Ebrey T, Koutalos Y (2001) Vertebrate photoreceptors. *Prog Retin Eye Res* 20:49–94
7. Granovsky AE, Natochin M, Artemyev NO (1997) The gamma subunit of rod cGMP-phosphodiesterase blocks the enzyme catalytic site. *J Biol Chem* 272:11686–11689
8. Schneeweis DM, Schnapf JL (1995) Photovoltage of rods and cones in the macaque retina. *Science* 268:1053–1056
9. He W, Cowan CW, Wensel TG (1998) RGS9, a GTPase accelerator for phototransduction. *Neuron* 20:95–102
10. Rebrik TI, Korenbrot JJ (2004) In intact mammalian photoreceptors, Ca^{2+} -dependent modulation of cGMP-gated ion channels is detectable in cones but not in rods. *J Gen Physiol* 123:63–75

Phrenic Nerve

Definition

Nerve innervating the diaphragm originating from C3 to C5 cervical cord.

▶ Hering-Breuer Reflex

Phrenology

Definition

Phrenology is an outdated field of study that proposed that mental functions could be related to the position of protuberances on the skull.

Phyletic Method

Definition

Uses cladistic methodology (cladograms, outgroup comparison) for establishing evolutionary polarity (i.e. ancestry vs. derivedness) of characters.

▶ Evolution of the Brain: In Fishes

▶ Evolution of the Telencephalon: In Anamniotes

Phylogenetic

Definition

Relating to or based on evolutionary development or history.

Phylogenetic Scale

► Evolution and the Scala Naturae

Phylogenomic Studies

Definition

Comparisons of whole genomes, or of large numbers of genes within genomes, to construct relationships among organisms.

Phylogeny

► Evolution and Phylogeny: Chordates
► Evolution and Phylogeny of Vertebrates

Phylogeny and Evolution of Chordates

► Evolution and Phylogeny: Chordates

Physical Exercise

► Stress Effects During Intense Training on Cellular Immunity, Hormones and Respiratory Infections

Physicalism

BARBARA MONTERO

Graduate Center, City University of New York,
New York, NY, USA

The Basic Formulation

The predominant philosophical theory about the world and our place in it is physicalism, the view, simply put, that everything is physical. In many circles, physicalism is not so much taken as the subject of debate but is rather assumed as the starting point around which other debates evolve. For example, a central problem in philosophy of mind is how to understand the mental given the truth of physicalism. But what, exactly, is the theory of physicalism? The simple formulation of physicalism as the view that everything is physical admits a number of interpretations, indeed, each term – “everything,” “is,” and “physical” – can be understood in different ways. To understand physicalism, then, let us look at these three aspects of the physicalist doctrine.

Scope

For some, physicalism is a theory about everything whatsoever, where “everything” is interpreted in its broadest sense to include, for example, concrete objects such as rocks and trees, abstract objects such as numbers and sets, properties such as the property of being conscious, events such as the event of my thinking about philosophy, even God, if She exists.¹ Others, however, think that arguments for physicalism have to be restricted to a certain scope? go only so far and restrict its scope accordingly. For example, some take physicalism as a theory only about the concrete world, that is, roughly about phenomena² in space or time.³ Others take it to be a theory about the empirical world, that is, about the phenomena that we come to know via our senses, or to put it more carefully, about the phenomena, the knowledge of which is justified via our sense experience. Still others take it to

¹ Or at least this is one way to state it. As a matter of terminology some physicalists reserve the term “physical” for the fundamental entities and properties of physics. Physicalism, on their view, can be true even if not everything is physical (in the narrow sense specified above), as long as everything nonfundamental is related to the physical (again, in the narrow sense) in the right way.

² I use “phenomena” in the broadest sense to include whatever exists.

³ The idea that the concrete also includes anything that is either spatial or temporal is important since if it were to include only the spatio-temporal than a disembodied nonspatial soul would not count as a counterexample to physicalism.

be a theory about or the contingent world, or the causal world, or the contingent and/or causal world.

How one restricts the scope of physicalism depends on one's purposes. And since the main physicalist target is typically the mental, it is not unusual to simply focus on the question of whether the mental is physical, or in other words, focus on physicalism with respect to the mental. Indeed, it is not unusual to see the theory that the mental is physical simply referred to as "physicalism." While "physicalism" in this sense refers just to the theory that the mental is physical, a more encompassing type of physicalism is sometimes evoked to justify physicalism with respect to the mental. One finds this when physicalists argue, that the mental is very likely to be physical because everything else is physical. Here, again, one wants to know, "just what is the scope of everything else?"

In considering physicalism about the mental, one sometimes finds another sort of restriction. While typically, philosophers speak of physicalism with respect to the mental as the view that all mental properties, such as the property of feeling pain, or seeing red, are physical properties, occasionally physicalism is taken to be a theory only about things and not about properties. For example, some will claim that the view that human beings are physical things with nonphysical properties is consistent with physicalism. Most, however, would take this to be an anti-physicalist view; if physicalism is true, all properties must be physical.

The view that all properties are physical is taken to imply the view that all entities are physical. The idea being that if all of your properties are physical, then you are physical.

Let us say, then, that physicalism in the broad sense is the view that everything, or some substantial subset of everything, is physical; in the narrow sense it is the view that all mental properties are physical.

The Dependence Relation

When the physicalist claims everything is physical or that all mental properties are physical properties, what is being said of everything or of all mental properties? Typically something is taken to be physical if its existence depends in the right way on basic or fundamental physical properties, where the fundamental physical properties are taken to be the microphysical properties countenanced by physics, such as the property of having a charge, of being a quark, and so forth. But what exactly is the [relation](#) between the fundamental physical properties and the higher level properties, such as mental properties, that suffices to make the higher level properties count as physical. In other words, when we say that everything is physical, just what is meant by "is?"

Some hold that the relation between higher level properties and fundamental physical properties is that of explanation. On this view it is thought that physicalism is true only if everything is either a fundamental physical

property or law, or it can be explained in terms of such properties and laws. As such, physicalism is an epistemic thesis that is, a thesis about what we know about the world rather than a thesis about what the world is really like. Still, it may have ontological implications since typically we think that a good indication of whether the fundamental nature of r is p is that we can explain r in terms of p .

Most philosophers, however, see physicalism primarily as an ontological thesis, a thesis that tells us about what the world is like. For this reason dependence relations are typically not formulated in terms of explanation, but rather in terms of supervenience, determination, realization, or constitution. Let us look at these relations.

Supervenience-physicalists hold that physicalism is true if everything either is a fundamental physical phenomenon or supervenes on fundamental physical phenomena. In terms of physicalism with respect to the mental, the view is simply that the mental supervenes on the fundamentally physical.⁴ What is the relation of supervenience? There are actually many supervenience relations and a large literature discussing them. The basic idea, however, is this: to say that A properties supervene on B properties, means that there cannot be a change in A properties without a change in B properties. So, for example, mental properties are said to supervene on fundamental physical properties if and only if there cannot be a change in mental properties without a change in fundamental physical properties. If your mood changes from being happy to being sad, for example, supervenience implies that there must be a change in your fundamental physical properties as well. Sometimes, the idea is explained in terms of mind and brain: when you change from feeling happy to sad, supervenience physicalism says there must be a change in your neural structure. But since a neural change, must ultimately involve a change the fundamental level, the idea amounts to the same thing.

Is supervenience physicalism really physicalism? Some think not since it seems that one kind of property could supervene, in this sense, on another kind of property yet be utterly different in kind from that property. For example, epiphenomenalism, a type of antiphysicalism, states that pain is a nonphysical property, which nonetheless supervenes on properties of the brain. Pain, on the epiphenomenalist view, is caused by the brain yet is utterly distinct from it and has no causal influence on it. Because of concerns such as these, supervenience is often thought of as merely a necessary condition for physicalism.

Philosophers who are looking for a sufficient condition for physicalism often turn to the relations of determination, constitution, and realization. While differing in details, these relations are all supposed to capture the idea that while the higher level properties,

⁴ What if there is no fundamental level? Physicalism needs to be reformulated. I address this in the next section.

such as mental properties, are not identical to certain lower level properties, such as neural properties, they are still not entirely distinct from these properties. The determination relation between the mental and the physical is something like the relation between, say, Mt. Everest and the little pebbles that constitute it. Mt. Everest is arguably entirely determined by its parts (once you have all the little pebbles, you have the mountain) and in this sense it is not distinct from its parts. Yet nonetheless, it might be argued, it is not identical to its parts since you could easily substitute one pebble from another mountain for a pebble from Mt. Everest without turning Mt. Everest into a different mountain. As we say that Mt. Everest is constituted or determined by its parts, the physicalist says that the mind is entirely constituted or determined by its physical parts.

Often the physicalist's claim is spelled out in terms of a thought experiment about the creation of the world. Imagine that in the beginning God created all the fundamental particles of physics and set them in motion according to a plan. If after creating the quarks and leptons and so forth and making sure that their patterns of motion were in accord with certain laws, would God have more work to do? For example, would she also need to create human minds? Physicalists think not since they think that the world we are familiar with, which includes rocks and trees and people with thoughts, is entirely constituted by complex arrangements of microphysical particles. This is not to say that physicalists must hold that there is nothing but complex arrangements of microphysical particles. Rather, most physicalists hold that higher level features of the world, such as rocks and trees and minds, do exist. It is just that the higher level features of the world are created in creating all of the microphysical aspects of the world.⁵

The Physical

Now we must address the question of what is the physical? When we say, for example, that everything is determined by fundamental physical phenomena what are these fundamental physical phenomena? As I said above, most define the fundamental physical in terms of the entities and properties and perhaps laws posited by microphysics: the fundamental physical phenomena are

those entities and properties mentioned in the theories of microphysics. But what is meant by microphysics? Some take microphysics to refer to current microphysical theory. This gives us a relatively clear position: physicalism becomes the view that everything that exists either is or is determined by the entities, properties, and laws of current microphysics. Unfortunately, this is a theory that is rather difficult to accept since we know that current microphysics is most likely neither entirely true nor complete and thus we know now that it is not true that everything is determined by such phenomena.

Because formulating the microphysical in terms of current microphysics leads to a theory we currently know is false, most physicalists formulate physicalism in terms of a true and complete microphysics. As such, physicalism is the view that everything will be accounted for by the entities and properties of a true and complete microphysics. But what is a true and complete microphysics? It would seem to be a theory that tells us about the fundamental nature of everything. But if so, physicalism turns out to be true by definition since the fundamental nature of everything, of course, will be accounted for by a theory that accounts for the fundamental nature of everything. While there is nothing necessarily wrong with being true by definition, most philosophers working on the question of physicalism do not think that at this point in the debate the truth of physicalism simply follows from its definition. Rather, most think that physicalism requires argument and empirical support, support which they speculate is forthcoming.

If we can neither formulate physicalism in terms of current physics nor in terms of a true and complete physics, how are we to formulate physicalism? It is not clear that we can formulate physicalism so as to assign pride of place to physics, however, we can reformulate physicalism with respect to the mind so that it captures at least most of what physicalists and antiphysicalists think is at issue. This is done by turning physicalism into a thesis not about the fundamental physical aspects of the world, but rather about the fundamental non-mental aspects of the world. Physicalism with respect to the mind then amounts to the view that all mental properties are determined by nonmental properties. One way to think about this view is that the mind is physical if all mental properties are determined by neural properties (couldn't a physicalist concede that some mental properties may be determined by other physical properties, say those of silicon chips?) and neural properties are themselves ultimately determined by non-mental properties.⁶

⁵ I have not discussed questions of the modality of the determination relation. Most physicalists think that physicalism could have been false, that God could have created nonphysical minds along with the creation of the fundamental physical particles, but some think of it as a necessary truth, that it is not possible that there could have been anything nonphysical. Moreover, while most think that physicalism could have been false, they also presumably think that it is not just by chance that it is true in our world; that is, they would deny that our world is such that if, say, two kinds of substances, which had never been brought together, were brought together, they would produce a nonphysical substance. In this sense, the creation thought experiment does not quite capture the content of physicalism.

⁶ This formulation would not be acceptable to an externalist, that is to someone who thinks that some mental content depends on features of the world outside of the brain. Externalists, then must rely on the more general formulation of physicalism as the view that all mental properties are determined by nonmental properties.

This way of formulating physicalism captures a central point of contention between physicalists and antiphysicalist: whether mentality is a fundamental feature of the world. But what if there is no fundamental level of reality? For example, if mental properties are determined by non-mental properties, which are themselves determined by mental properties, which are determined by non-mental properties and so on *ad infinitum*, or if it is mental “all the way down,” then, in either case, all fundamental properties are non-mental properties, vacuously, since there are no fundamental properties, yet physicalists would probably want to reject these world views. To address this issue, we can formulate physicalism with respect to the mental as the view that *all mental properties are eventually decomposable into non-mental properties such that all further decompositions of these properties are non-mental*.

As a general theory of physicalism, that is, as theory about the nature of everything, this formulation is inadequate. This is because there may be phenomena that for certain purposes would be unacceptable yet are nonmental. For example, a world with fundamental moral properties or abstract entities would seem to be inconsistent with physicalism, yet such things are not mental. That there is no general theory of physicalism, however, does not mean that much interesting work cannot proceed on specific topics, including questions about the ultimate nature of the mind.

- Causality
- The Knowledge Argument

Physiological Cell Death

- Programmed Cell Death

Physiological Pain Parameters

Definition

Physiological pain measures include heart rate, respiration rate, blood pressure, palmar sweating, cortisol and cortisone levels, O₂ levels, vagal tone and endorphin concentrations. They are indirect pain measures and reflect a complex and generalized stress response, rather than correlate with a particular pain level.

- Pain in Children

Physiology of Body Fluid Balance

- Blood Volume Regulation

Pia Mater

Synonyms

- Meninges; ► Cisterns

Definition

Together with the arachnoid, the pia mater forms the leptomeninges.

Whereas the arachnoid follows the course of the dura mater and hence of the calvaria, the pia mater rests on the surface of the brain, pursuing a joint course along the sulci. Lying between the pia mater and arachnoid is the subarachnoid space that is filled with CSF.

Pick's Disease

Definition

Pick's disease is a severe neuro-degenerative disease in the neocortex of the ► [frontal lobe](#) and anterior ► [temporal lobe](#), and at times of neurons in the ► [striatum](#).

Pickwickian Syndrome

Definition

Named after a Charles Dickens tale involving a character with clinical signs of the syndrome of obstructive sleep apnea and obesity hypoventilation.

The combination of upper airway obstruction and reduced lung volumes from the restrictive ventilatory effect of obesity causes low blood oxygen and elevated carbon dioxide, with their associated physiological consequences.

- Sleep – Developmental Changes

PID Control

Definition

A popular closed-loop control method that uses a simple (Proportional-Integral-Derivative) linear controller with easily tunable parameters.

► Nonlinear Control Systems

Piloerection or Pilomotor Reflex

Definition

Piloerection or pilomotor reflex, also called horripilation, consists of involuntary hair erection induced by contraction of arrectores pilorum muscles, i.e., the tiny muscles located at the origin of each body hair. It is a reaction to cold temperature or strong emotions producing the so-called cutis anserina or goose bumps/pimples. Arrectores pilorum muscles receive the contractile command by the sympathetic nervous system.

► Sympathetic Nervous System

Pineal Body

Synonyms

► Glandula pinealis; ► Pineal gland

Definition

This nuclear region, shaped like a pine cone, above the quadrigeminal lamina forms, together with the habenular nuclei, the so-called epithalamus. The function of the pineal body, also called epiphysis or pineal gland, is to produce the hormone melatonin, which plays a role in light-controlled circadian rhythms. Afferents come from the suprachiasmatic nucleus, pre-geniculate nucleus and posterior commissural nucleus.

► Diencephalon

Pineal Gland

Definition

The pineal gland (or the epiphysis cerebri, or epiphysis) is an endocrine gland located in the brain. The primary role of the pineal gland is the synthesis and release of the hormone melatonin. This hormone plays an important role in the regulation of many neurobiological aspects (e.g., circadian rhythms, sleep and reproduction).

The pineal gland receives a sympathetic innervation from the superior cervical ganglion. In nonmammalian vertebrates the pineal gland is directly photosensitive and usually contains circadian oscillators.

► Avian Pineal Gland as “Third Eye”

► Pineal Oscillators

Pineal Hormone

► Melatonin

Pineal Oscillators

Definition

In many animals the pineal gland contains circadian pacemakers that directly control the synthesis of melatonin. A single pineal cell (pinealocyte) is capable of driving the circadian rhythms in melatonin release.

Therefore, it is composed of many “clocks” that are capable of producing a synchronized output (melatonin).

Indeed, in birds and in many non-mammalian vertebrates, the pineal gland acts as a circadian pacemaker that regulates the entire circadian system.

In mammals the pineal gland does not contain circadian oscillators. However, recent studies have reported that the mammalian pineal gland may also contain a circadian clock, although this circadian oscillator does not regulate melatonin synthesis and, therefore, its functional role is unclear.

► Circadian Rhythm

Pinealectomy

Definition

Surgical removal of the pineal gland.

► [Seasonality](#)

Pioneer Axons

Definition

Pioneer axons are the first axons to extend into novel regions of the developing embryo. Growth cones of pioneer axons generally have a broad hand-like appearance with filopodia, consistent with making guidance choices based on cues in the environment.

Later growing axons will often fasciculate with these pioneer axons and use them as tracks on which to grow to their target region. In most of the embryo, motor neurons of the CNS send out the pioneer axons traveling to peripheral structures and sensory axons later grow along these tracks. However, in the developing head, sensory ganglion neurons send out the pioneer axons and motor axons later travel along these tracks.

► [Growth Cones](#)

Piriform Cortex

Definition

The allocortical piriform cortex (also termed olfactory or pyriform or prepiriform cortex) is the largest primary area involved in the perception and learning of olfactory stimuli. It is located in the rostral part of the forebrain, ventrally to the rhinal sulcus, and it is reciprocally connected with other olfactory regions and with high order brain areas. It is commonly divided in two regions (an anterior and a posterior part) which are believed to have different functional roles.

► [Olfactory Cortex](#)

Pit Organ

Definition

Receptor of infrared radiation, pits near the nostrils, actually primitive “eyes,” which register not only the heat, but also the direction of its source, e.g. a small rodent.

► [Evolution of the Brain: At the Reptile-Bird Transition](#)

Pituitary Adenylate Cyclase-Activating Polypeptide1 (PACAP)

Definition

Neuropeptide involved in the phase shift response of the circadian clock in response to nocturnal light and also stimulates the release of melatonin from the adult pineal gland.

► [Clock-Controlled Genes](#)

Pituitary Gland

Definition

Also called hypophysis. The pituitary gland is an appendix to the hypothalamus at the base of the forebrain. The pituitary consists of an anterior adenohypophysis and a posterior neurohypophysis.

The hypothalamus emits a number of releasing hormones and release-inhibiting hormones, which regulate the release of hormones from the adenohypophysis.

- [Hypophysis](#)
- [Hypothalamo-neurohypophysial System](#)
- [Hypothalamo-pituitary-adrenal Axis, Stress and Depression](#)
- [Hypothalamo-pituitary-thyroid Axis](#)
- [Hypothalamus](#)
- [Releasing-Hormone and Release-Inhibiting Hormone](#)

PKA

Definition

►Protein Kinase A

PKC

Definition

►Protein Kinase C

Place Cells

Definition

Neurons discharging selectively when the subject is in a delimited region of its environment referred to as a “firing field” or “place field.” First discovered in the hippocampus by O’Keefe and Dostrovsky (1971).

Found in rats, mice, birds, bats, and primates including humans. Although most observers agree that the hippocampus has a critical role in learning and memory, there remains considerable debate about the precise functional contribution of the hippocampus to these processes.

Two of the most influential accounts hold that the primary function of the hippocampus is to generate cognitive maps and to mediate episodic memory processes. The well-documented spatial firing patterns (place fields) of hippocampal neurons in rodents, along with the spatial learning impairments observed with hippocampal damage support the cognitive mapping hypothesis. The amnesia for personally experienced events seen in humans with hippocampal damage and the data of animal models, which show severe memory deficits associated with hippocampal lesions, support the episodic memory account.

- The Hippocampus: Organization
- Neural Bases of Spatial Learning and Memory
- Hippocampus: Organization, Maturation, and Operation in Cognition and Pathological Conditions

Place-versus-Response Controversy

Definition

This controversy was a well-known debate among groups of psychologists in the early twentieth century.

The response group (behaviorists) felt that all behavior, including navigation, must be described in simple stimulus-response terms. The place group (cognitivists) felt that complex behavior could only be explained by positing that the rat brain contained a central representation – a map of the places in the environment.

►Spatial Learning/Memory

Placebo Analgesic Response

HOWARD L. FIELDS

Ernest Gallo Clinic and Research Center, University of California, San Francisco, USA

Synonyms

Expectancy effect; Palliative; Dummy treatment; Control treatment

Definition

The ►placebo analgesic response is a reduction in ►pain resulting from the recipient’s expectation that a treatment received has analgesic efficacy. The term placebo is usually used when the treatment is intentionally given deceptively and has no intrinsic analgesic efficacy.

Characteristics

Some individuals experience a reduction of their pain when they are given a completely inert substance with the understanding that it is an effective treatment. If the person giving it knows that the treatment is inert (i.e., it is given with the intention to deceive the recipient), the treatment is a placebo. However, even if the individual receiving the placebo experiences a reduction in their pain following placebo administration, it is not necessarily the case that the placebo caused the reduction. The reason for the uncertainty is that in clinical syndromes it is common to observe frequent fluctuations in pain over time in the absence of any treatment. This fluctuation is called the ►natural history of the painful condition. Consequently, one cannot conclude that a given instance of a reduction in pain is due to the preceding treatment manipulation,

whether placebo or active medication. Because of this uncertainty, well designed clinical trials of analgesic medications generally require a comparison group receiving placebo treatment. The efficacy of an analgesic medication is established by showing that it produces a reduction in pain superior to placebo.

This uncertainty about the cause of a fluctuation in pain also presents challenges for research into the mechanisms underlying the placebo analgesic response [1]. One obvious difficulty is that if the individual improves, it is uncertain whether it is because of a placebo analgesic response or would have occurred in the absence of treatment. Thus, placebo analgesic responses in an individual are usually inferred, not observed. On the other hand, placebo analgesic effects are quite robust when studied comparing two *groups* of subjects, one of which receives a placebo and the other no treatment. The **▶placebo effect** in that situation is the difference between those two groups. The difficulty in identifying individual, as opposed to group placebo analgesic responses has made it very difficult to determine whether there are specific characteristics of individuals that make them more or less likely to respond to a placebo manipulation. On the other hand, comparing groups given placebo versus no-treatment has increased our understanding of the psychological and neural mechanisms of the placebo analgesic response.

In addition to its usefulness in controlled clinical trials, responses to placebo likely play a significant role in clinical practice. Placebo administration can provide effective relief for severe pain conditions, including those following major surgical procedures. It is also important to point out that even when effective analgesic agents are given to patients, part of the pain relief obtained may be due to a **▶placebo response**. For example, when a moderate dose of morphine is given to a pain patient by hidden infusion (i.e., from a preprogrammed remote pump at an unknown time), it is much less effective than when it is given openly. When patients with postoperative pain are told that they may receive morphine, but instead are given an open administration of saline through an intravenous catheter, they obtain pain relief equivalent to a moderate dose of morphine given by hidden infusion [2]. This suggests that in many cases the relief obtained when individuals take an analgesic agent is a sum of a placebo response plus the effect of the active agent.

Studies directed at the psychological determinants of the placebo response have identified **▶expectancy** as the most relevant psychological mediator. Expectancy can be manipulated verbally for example by simply informing the subject that the treatment they are about to receive is a powerful analgesic [3]. Expectancy can also be manipulated by explicit training, which leads to **▶conditioned memory**. One form of conditioning is to treat subjects in pain with a powerful analgesic agent and

subsequently administering a similar appearing placebo treatment to them [4]. Another approach is through surreptitiously lowering the intensity of an experimental painful stimulus in the presence of a placebo treatment [5] and then re-administering the placebo treatment. For either approach, the conditioning markedly increases the analgesic effectiveness of a placebo treatment. Furthermore, there is a clear relationship between the subject's expectations and the degree of relief experienced [5].

Progress has also been made in understanding the neural mechanisms underlying the placebo analgesic effect. One of the first mechanistic proposals was that expectation of reward somehow led to the release of endogenous **▶opioid peptides** which acted at **▶opioid receptors** in the central nervous system to produce analgesia. This idea was supported by the finding that placebo relief of dental postoperative pain could be blocked by the opioid receptor antagonist **▶naloxone** [6]. Naloxone was later shown to block placebo analgesia in experimental pain models in normal volunteers [7]. Furthermore, there is a central nervous system pathway that modulates pain transmission (see **▶Descending modulation of nociception**). This pathway is organized in a top-down fashion. It includes the **▶anterior cingulate cortex** and other regions of the **▶prefrontal cortex**, the **▶hypothalamus**, **▶amygdala** and brainstem and it terminates in the **▶spinal cord** [8]. The anterior cingulate cortex and other prefrontal areas have been implicated in expectancy effects including placebo analgesia. Furthermore, endogenous opioid peptides are released throughout this pathway and contribute to its analgesic effects. Human **▶functional imaging** studies, including both **▶positron emission tomography** and **▶functional magnetic resonance imaging**, have provided evidence that supports a role for this **▶pain modulating pathway** in placebo analgesia. Placebo analgesic effects correlate with activation of prefrontal cortex and brainstem regions areas that overlap with the endogenous opioid mediated **▶pain modulatory pathway** [9,10].

In summary, the expectation of pain relief, whether induced by verbal instruction or conditioning, can bestow robust analgesic potency on a treatment that would otherwise be ineffective. The expectancy effect is mediated by a pain modulating pathway with endogenous opioid links. Placebo analgesic responses may also contribute to the efficacy of active analgesic agents through summation with direct drug effects.

References

1. Amanzio M, Benedetti F (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 19:484–494
2. Benedetti F, Amanzio M (1997) The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog Neurobiol* 52:109–125

3. Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C (2006) Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. *Pain* 120:8–15
4. Fields HL, Basbaum AI, Heinricher MM (2006) Central nervous system mechanisms of pain modulation. In: McMahon SB, Koltzenburg M (eds) *Wall and Melzack's Textbook of pain*, 5th edn. Elsevier Churchill Livingstone, Edinburgh, pp 125–142
5. Hoffman GA, Harrington A, Fields HL (2005) Pain and the placebo: what we have learned. *Perspect Biol Med* 48:248–265
6. Levine JD, Gordon NC, Fields HL (1978) The mechanism of placebo analgesia. *Lancet* 2:654–657
7. Levine JD, Gordon NC, Smith R, Fields HL (1981) Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain* 10:379–389
8. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F (2001) Response expectancies in placebo analgesia and their clinical relevance. *Pain* 93:77–84
9. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS (1999) An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 83:147–156
10. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD (2004) Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 303:1162–1167

Planes of Section

Definition

Planes of section are usually expressed in relation to the upright midline axis of the body (or spinal column). The plane of section that passes through or parallel to the midline and extends in the dorsal-ventral direction is the sagittal plane. Parasagittal planes pass to the left or to the right of the midline sagittal plane that is marked by the sagittal suture of the skull. The horizontal plane is at a right angle to the sagittal plane and parallel with the ground. Horizontal planes progress inferiorly or superiorly. The frontal (coronal) plane is orthogonal to the other two. It is in the plane of the coronal suture of the skull. Frontal planes progress anteriorly and posteriorly.

Plant

Definition

The external environment that needs to be controlled, e.g. an arm.

► Neural Networks for Control

Plasma Membrane

Definition

► Cell Membrane Components and Functions

Plasma Membrane Ca^{2+} -ATPase (PMCA)

Definition

A pump on the plasma membrane that couples ATP hydrolysis to the extrusion of Ca^{2+} from the cytosol to the extracellular space.

► Influence of Ca^{2+} Homeostasis on Neurosecretion

Plasmalemma

Definition

The term denotes the cell membrane separating the interior from the exterior of a cell except in muscle cells, where the cell membrane is called “sarcolemma.”

► Cell Membrane Components and Functions

Plasmid Vector

Definition

Small circular molecules of double stranded DNA derived from natural plasmids found in bacteria. They themselves are distinct from the chromosomal genome of bacteria. An exogenous piece of DNA can be easily inserted into a plasmid if both the plasmid and the exogenous DNA source have recognition sites for the same restriction endonuclease.

► Serial Analysis of Gene Expression

Plasticity

Definition

The ability of the brain to change its functional organization and neural representations (e.g. motor and sensory maps) as a result of damage or experience and in response to altered peripheral conditions or behavioral demands.

- ▶ **Motor Cortex – Hand Movements and Plasticity**
- ▶ **Somatosensory Cortex, Plasticity**

Plasticity in Central Auditory System

DEXTER R. F. IRVINE

Department of Psychology, Monash University,
VIC, Australia

Definition

Changes in the structural and functional characteristics of neurons in the central auditory system (CAS), which occur in response to altered patterns of input (i.e., not as a direct consequence of aging or of other changes in the organism's state), and are not explicable as passive consequences of the altered input, but involve some form of dynamic change in neural properties [1].

Characteristics

Higher Level Structures

The CAS comprises the various ▶ **auditory subcortical nuclei** and the multiple cortical fields that comprise the auditory cortex (▶ **auditory cortical areas**), together with the (ascending and descending) pathways that link these structures.

Lower Level Components

The lower level components are the individual neurons and their processes that make up the various nuclei and fiber tracts comprising the CAS, the synaptic connections between these neurons, and the networks they comprise.

Higher Level Processes

CAS plasticity has been demonstrated in a variety of experimental conditions, and is assumed to underlie a number of forms of auditory behavioral plasticity; however, it is by no means clear that the same mechanisms are involved in all cases. A broad distinction can be made between forms of plasticity that occur

only during development (in many cases within restricted ▶ **critical periods**), and those that are observed in both young and adult animals. In the following sections, the major paradigms that have been used to study developmental and adult plasticity will be briefly reviewed.

Developmental Plasticity: Neonatal Cochlear Ablation

Neonatal ablation of one ▶ **cochlea** in mammals, which eliminates afferent input from that ear to ▶ **binaural neurons** in the CAS, results in structural and functional changes in the input from the intact ear to these neurons. Axons from the ventral division of the ▶ **cochlear nucleus** (CN) on the side of the intact ear, which normally terminate in restricted regions of the major nuclei of the ▶ **superior olivary complex**, project to, and make synapses in, regions of these nuclei normally innervated by the CN on the side of the ablated cochlea. Similarly, the terminal fields in the central nucleus of the ipsilateral ▶ **inferior colliculus** (IC) of axons from the CN on the side of the intact ear are much larger than those in normal animals [2]. Both of these results indicate that, following unilateral cochlear ablation, axons from the CN on the intact side sprout to innervate additional territory. These structural changes are associated with increased excitatory responses to stimulation of the intact ear in the ipsilateral IC and ▶ **primary auditory cortex** (AI) [2].

Developmental Plasticity: Space Map Plasticity

In barn owls, and in at least some mammals, the deep layers of the ▶ **superior colliculus** (SC) contain maps of auditory and visual space that are in register (i.e., bimodal neurons, or auditory and visual neurons at the same locus, have corresponding auditory and visual ▶ **spatial receptive fields** (RFs)). The auditory ▶ **space map** is derived via orderly projections from the ▶ **external nucleus of the** (ICX), and is based on neural sensitivity to ▶ **interaural time and level differences** (ITDs and ILDs, respectively) and, in mammals, on sensitivity to ▶ **spectral cues** produced by the effects of the head and ▶ **pinnæ** on the sound field [2]. In both barn owls [3] and ferrets [2] reared from infancy with one ear plugged (thus altering the values of the interaural disparities associated with any given spatial location), the visual and auditory maps are in register. In the barn owl, this reflects the fact that the tuning to ITDs and ILDs of neurons in ICX and SC has changed to maintain alignment of the auditory and visual RFs. This change in neural tuning is associated with the appearance of novel projections from the central nucleus of IC (ICC) to ICX: axons sprout into, and form synapses in, regions outside their normal projection zone [3]. Immediately after ear plugging, young owls mislocalize sounds, but in parallel with the map changes, they recover accurate localization ability. Ear plugging in adult animals does not result in adaptive changes in interaural

disparity tuning, and the auditory and visual space maps therefore remain out of register while the plug is in position. Analogous developmental plasticity occurs when owls are raised wearing prismatic spectacles that displace the visual field in the horizontal plane: the tuning of SC neurons to ITDs (which serve as the cue for azimuthal location in barn owls) shifts to maintain the correspondence between auditory and visual RFs [3]. The plasticity demonstrated in these studies using experimental manipulations of sensory input occurs in all animals during development as the size of the head increases, and the values of ITDs and ILDs associated with particular spatial locations consequently change.

Adult Plasticity: Injury-Induced

Lesions of a restricted region of the cochlea (which result in a partial hearing loss) result in a reorganization of the ►frequency map in AI. The nature of this reorganization is that the region deprived of its normal input by the cochlear lesion is occupied by an expanded representation of the frequencies represented at the edge(s) of the cochlear lesion. The thresholds, latencies, and sharpness of ►frequency tuning of neurons in this expanded representation at their new ►characteristic frequency (CF) indicate that the changed frequency organization is not a passive consequence of the peripheral lesion, but reflects a dynamic process of reorganization. Such reorganization is observed after mechanical cochlear lesions, and after lesions produced by ►ototoxic drugs or by ►noise trauma [1]. Analogous reorganization is seen in visual and somatosensory cortices after restricted retinal lesions and digit amputation, respectively [4]. After mechanical cochlear lesions, similar reorganization is seen in the major auditory thalamic nucleus (the ventral division of the ►medial geniculate nucleus), but reorganization is patchy in the ICC and is not observed in the dorsal nucleus of the CN, suggesting that this form of CAS plasticity is a characteristic of ►thalamo-cortical circuitry.

Adult Plasticity: Learning-Induced

Changes in the stimulus selectivity of neurons in the higher levels of the auditory pathway, as a consequence of behavioral conditioning procedures in which an acoustic stimulus serves as the ►conditioned stimulus or discriminative (henceforth “training”) stimulus, were the first demonstrations of CAS plasticity in adult animals, and this remains the most active area of research on this topic. The most common finding in these studies is that the response of cortical neurons at the training frequency increases, while the response at other frequencies decreases, such that the training frequency becomes the neurons’ ►best frequency. Such effects have been described in AI and in secondary auditory cortical fields, and in the auditory thalamus [1,5,6]. These studies have commonly used ►fear

conditioning procedures, but appropriate controls, and the specificity of the effects to the training frequency, establish that the observed effects are manifestations of plasticity rather than consequences of changes in state variables [6]. A substantial body of evidence indicates that the ►cholinergic basal forebrain plays an important modulatory role in this form of CAS plasticity [1].

Another form of auditory learning that might involve CAS plasticity is ►perceptual learning, the improvement in discriminative capacity with training that is a common observation in all sensory modalities both in psychophysical experiments and in everyday life [1,7,8]. The specificity of many forms of visual perceptual learning to particular features of the training stimuli, or to the region of the receptor to which the stimuli are presented, has led to the proposal that the learning might involve changes in neural tuning in primary sensory cortex [7,8]. In the auditory system, the evidence for changes in AI associated with perceptual learning is equivocal [7], and it is possible that the learning involves changes in higher-order decision making processes. Indirect evidence for auditory cortical changes is provided by ►functional imaging evidence of larger auditory cortical responses to musical tones in trained musicians, although in this case it is not clear whether the larger cortical responses are a consequence of training, or whether people with this innate characteristic are more likely to undertake such training [1].

Two forms of auditory perceptual learning that are of great practical significance relate to speech processing. The first is the effect of language experience on the perception of speech sounds, and thus on language acquisition, during a critical period of development [9]. The second is the improvement in speech discrimination shown by people with ►cochlear implants over the months and years following implantation. Whether these forms of learning reflect plasticity in the CAS itself or in regions involved in cognitive processes is not clear.

Adult Plasticity: Microstimulation-Induced

A series of studies in adult bats and gerbils have indicated that focal electrical stimulation of a region of AI can change the frequency selectivity of neurons around the stimulation site in AI, and in the tonotopically corresponding area of the central nucleus of the IC [5]. ►Centrifugal fibers from AI to IC have been shown to play a role in this plasticity.

Lower-Level Processes

The cellular mechanisms of CAS plasticity (and those of plasticity in other sensory systems) are incompletely understood. Different forms of plasticity have different time courses, as do different phases of particular forms of plasticity. The first stage of injury-induced plasticity

in sensory cortices appears to be an expansion of RFs, reflecting an unmasking of normally-inhibited excitatory inputs from outside the classically defined RF [10]. A similar unmasking is involved in space map plasticity in the barn owl [3]. The subsequent establishment of smaller RFs in injury-induced plasticity presumably involves changes in the efficacy of both excitatory and inhibitory synapses, and there is evidence for the strengthening of excitatory synapses via ►NMDA-receptor mediated ►long-term potentiation in developmental plasticity in the barn owl [3] and in adult plasticity in the visual and somatosensory systems [10]. Longer-term changes in the barn owl involve axonal sprouting and ►synaptogenesis [3]; axonal sprouting is also involved in the changes observed after unilateral cochlear ablation in neonatal animals [2]. Axonal sprouting of horizontal fibers in the superficial layers of the cortex has also been shown to be involved in visual cortical plasticity after retinal lesions in adults [8]. Structural changes of this sort have not yet been shown in injury-induced auditory plasticity in adults. Finally, as mentioned previously, corticofugal projections have been shown to be involved in some forms of plasticity [5,8].

Function

Auditory developmental plasticity and learning-induced plasticity are undoubtedly adaptive, in that they enhance the organism's ability to adjust to altered patterns of input and, in the case of human language acquisition and adaptation to a cochlear implant, make important auditory discriminations. It is less-clear that adult injury-induced plasticity is adaptive, as the organism remains deaf in the frequency range affected by the cochlear lesion, and there is little evidence that the CAS reorganization consequent on the lesion in any way compensates for this deafness. It is likely that this form of plasticity is an extreme manifestation of the processes that underlie other forms of plasticity in response to altered input, but it is also possible that similar processes are involved in recovery of function after central damage such as that produced by stroke.

Pathology

There is little evidence that these forms of plasticity have pathological consequences, although it has been suggested that tinnitus might be a consequence of cortical reorganization consequent on a peripheral lesion [1].

Therapy

The possibility that some forms of learning impairment might involve deficiencies in aspects of auditory processing that exhibit plasticity, such that these deficiencies can be modified by training, has resulted

in the recent development of a number of auditory training software packages. As discussed previously, the success of cochlear implants undoubtedly rests in part on the plasticity of CAS structures, and plasticity therefore contributes to the therapeutic effects of these devices.

References

1. Irvine DRF, Wright BA (2005) Plasticity in spectral processing. In: Malmierca M, Irvine DRF (eds) Auditory spectral processing. Elsevier, San Diego pp 435–472
2. Moore DR, King AJ (2004) Plasticity of binaural systems. In: Parks TN, Rubel EW, Popper AN, Fay RR (eds) Plasticity of the auditory system. Springer, New York, pp 96–172
3. Knudsen EI (2002) Instructed learning in the auditory localization pathway of the barn owl. *Nature* 417:322–328
4. Kaas JH, Florence SL (2001) Reorganization of sensory and motor systems in adult mammals after injury. In: Kaas JH (ed) The mutable brain. Harwood Academic Publishers, New York, pp 165–242
5. Suga N, Ma X (2003) Multiparametric corticofugal modulation and plasticity in the auditory system. *Nat Rev Neurosci* 4:783–794
6. Weinberger NM (2004) Experience-dependent response plasticity in the auditory cortex: issues, characteristics, mechanisms, and functions. In: Parks TN, Rubel EW, Popper AN, Fay RR (eds) Plasticity of the auditory system. Springer, New York, pp 173–227
7. Irvine D, Brown M, Martin R, Park V (2005) Auditory perceptual learning and cortical plasticity. In: Koenig R, Heil P, Budinger E, Scheich H (eds) The auditory cortex: a synthesis of human and animal research. Lawrence Erlbaum, Mahwah, NJ, pp 409–428
8. Tsodyks M, Gilbert C (2004) Neural networks and perceptual learning. *Nature* 431:775–781
9. Kuhl PK (2000) A new view of language acquisition. *Proc Natl Acad Sci USA* 97:11850–11857
10. Calford MB (2002) Dynamic representational plasticity in sensory cortex. *Neuroscience* 111:709–738

Plasticity in Nociception

Definition

Plasticity with respect to nociception refers to modulation of nociceptive afferent signals. Plasticity with respect to pain refers to the modulation of pain perception. The biological response to tissue damage, and the subsequent perception of pain, can vary depending on activation of other ascending and descending sensory systems.

►Spinal Dorsal Horn Plasticity

Plateau Potential

Definition

A membrane potential depolarization that is sustained by intrinsic properties even after the stimulus that triggered it has been terminated. In contrast to a pacemaker potential, the plateau potential is not rhythmically activated and terminated by the neuron.

Instead, onset and termination of plateau potentials are typically triggered by excitatory and inhibitory synaptic inputs. Most commonly plateau potentials are caused by the action of persistent inward currents (e.g. persistent Na^+ current, low-voltage activated Ca^{2+} currents, etc.). Once these currents have been activated by a synaptic input or brief depolarization, the resulting inward current is sufficient to sustain the depolarization and maintain their activation. The depolarization can be terminated by inhibitory synaptic inputs that hyperpolarize the membrane potential sufficiently to remove the activation of the persistent inward current. The plateau potential can also be terminated by intrinsic mechanisms, e.g. persistent Ca^{2+} influx can activate Ca^{2+} -dependent K^+ channels that cause an outward current which will repolarize the membrane potential and terminate the plateau potential.

- Calcium Channels – an Overview
- Central Pattern Generator
- Neuronal Potassium Channels
- Sodium Channels

Play

- Learning and Motivation

PLC γ

Definition

Is a member of the Phospholipase C family that consists of PLC- Δ , - β , - γ and - ϵ which all require calcium for their catalytic activity. PLC γ is activated by transmembrane receptors with tyrosine kinase activity and is a key enzyme involved in the activation of protein

kinase C (PKC) leading to Akt activation and increased survival following axonal injury.

- Neurotrophic Factors in Nerve Regeneration

Plegia

Definition

Severe loss of motor strength by motor paralysis of entire limbs or parts thereof.

Plexus

Definition

A plexus (Latin for braid) is a region of exchange of nerve fibers of different spinal cord levels to form specific peripheral nerves.

PMBSF

- Barrel Cortex

Pneumotaxic Center

- Pontine Control of Respiration

PNS

Definition

Peripheral nervous system including cranial and spinal nerves.

p75NTR

Definition

p75NTR (p75 neurotrophin receptor) is a 75 kDa member of the Tumour Necrosis Factor (TNF) receptor family whose members share a cysteine-rich common extracellular binding domain. It was originally identified as a low-affinity receptor for NGF (nerve growth factor). It has since been shown that p75NTR binds all known members of the neurotrophin family (NGF, BDNF, NT-3, NT-4/5), and subsequent intracellular activation is upstream of both the PKC and JNK pathways resulting either survival or death. Denervated Schwann cells express high levels of p75NTR as a consequence of the loss of axonal contact. The function of p75NTR in Schwann cells is currently not known.

- Neurotrophic Factors in Nerve Regeneration
- Schwann Cells in Nerve Regeneration
- Tumor Necrosis Factor- α

Point Contacts

- Integrin-dependent Adhesion Contacts

Point-to-Point Movements

Definition

Point-to-point movements are a sequence of discrete movements, where each movement starts from one position aiming to a next position.

- Motor Control Models

Polar Decomposition Theorem

Definition

A theorem in linear algebra stating that every nonsingular square matrix is uniquely decomposable

into the product of an orthogonal matrix and a positive definite symmetric matrix.

- Mechanics

Polarity

Definition

Polarity in the case of neurons, polarity refers to the fact that neurons are polarized structures with an axon and dendrites.

Polarity of Neurons

Definition

In the case of neurons, polarity refers to the fact that neurons are polarized structures with an axon and dendrites.

Poles

Definition

The roots of the denominator of a transfer function.

- Signals and Systems
- Transfer Function

Polioencephalitis (Anterior Poliomyelitis)

Definition

Acute infectious viral disease affecting several parts of the central nervous system, classically involving spinal ► motoneurons with final degeneration and paralysis.

Poliomyelitis

Definition

Acute infectious disease of humans, particularly children, caused by any of three serotypes of the human poliovirus; infection is usually limited to the gastrointestinal tract and nasopharynx, and is often asymptomatic. The central nervous system, primarily the spinal cord, may be affected, leading to rapidly progressive ►paralysis, coarse fasciculation and ►hyporeflexia. ►Motoneurons are primarily affected, and ►encephalitis may also occur.

Poly(A) Tail

Definition

A polyadenosine tail is the product following polyadenylation of pre-mRNA. Most messenger RNA molecules end with a poly-A stretch at their 3' ends in eukaryotic organisms. The poly(A) tail protects mRNA from exonucleases and plays a role in transcription termination. Typically 50–200 adenosines are added to pre-mRNA.

►Serial Analysis of Gene Expression

Polyadenylation

Definition

Polyadenylation is a covalently-linked tail of a long stretch of adenosines added to the 3' end of the mRNA, and is required to generate mature mRNA.

Polydipsia

Definition

A symptom in which the patient ingests abnormally large amounts of fluids.

►Neuroendocrinology of Psychiatric Disorders

Polyhydramnios

Definition

Increased amounts of amniotic fluid.

►Endocrine Disorders of Development and Growth

Polymer

Definition

A compound consisting of many repeated linked units.

Polymerase Chain Reaction (PCR)

Definition

Polymerase chain reaction (PCR) is used to isolate and amplify in an exponential fashion a DNA sequence of interest. mRNA is isolated from a cellular or tissue source, a cDNA copy is made by reverse transcriptase, and the DNA found between a 3' and a 5' nucleotide single strand DNA primer (complementary DNA sequence) is amplified by approximately 20–30 cycles that include denaturation of double stranded DNA, annealing of the primers to the cDNA, and DNA synthesis.

Polymodal

►Multimodal Integration

Polymodal Receptor

Definition

Polymodal receptor denotes a sensory receptor (e.g. nociceptor) responsive to more than one modality or sub-modality (quality), e.g. to pressure, temperature

and/or certain chemical substances. Polymodality is also prevalent in central neurons.

- Nociceptors and Characteristics
- Sensory Systems

Polymorphic Network

Definition

A neuronal network that can change its functional connectivity in response to modulatory influences by higher order interneurons. Modulatory interneurons can enhance or suppress the function of individual synapses and neurons within a network. This can result in the functional removal or addition of neurons to a neuronal network, which leads to the reconfiguration of the network.

- Central Pattern Generator

Polymorphism

Definition

Sequence variants that exist naturally in the population and that do not cause disease. Polymorphisms account for all interpersonal variation (e.g., height, eye, skin and hair color, etc.)

- Bioinformatics

Polymyositis Syndrome

Definition

Inflammatory myopathy prevailing in proximal muscles and resulting in weakness.

Polyneuropathy

Definition

Disease affecting many nerves.

Polypeptide

- Neuropeptides in Energy Balance

Polypeptide Synthesis

- RNA Translation

Polyradiculopathy

Definition

Disease of many spinal nerve roots.

Polyribosomes

Definition

Polyribosomes are multiple ribosomes attached to a single messenger RNA (mRNA) molecule. The ribosomes translate the information encoded on the mRNA into a protein.

- Extrasomal Protein Synthesis in Neurons

Polysomnogram

Definition

A sleep monitoring technique combining electrophysiological technologies to determine sleep stages and other sleep phenomena. Minimally, polysomnography (PSG) includes the electroencephalogram (EEG) to record electrical activity in the brain; the electrooculogram (EOG) to record eye movements; and the electromyogram (EMG) to record muscle tone. More extensive montages including electrocardiography (ECG) and measurements of airflow, breathing effort, body position, snoring sounds, and blood oxygen saturation are used for the diagnosis and treatment of disorders of sleep.

- Alertness Level
- Brain States and Olfaction

- ▶ Electroencephalography
- ▶ Electromyography
- ▶ Electrooculography

Polysynaptic Accessory Olfactory System

- ▶ Accessory Olfactory System

Pons (Varolius)

Definition

The pons (Latin for bridge, describing the large fiber bundle running across the ventral surface of the brainstem, perpendicular to its long axis) is the portion of the brainstem between the medulla and midbrain. The cerebellum sits dorsal to the pons and is attached to it by the large fiber bundles of the middle cerebellar peduncle on each side. The pons consists of two parts: base of pons and tegmentum. The typical protruding base of pons accommodates the pyramidal tracts. Interspersed here are the pontine nuclei, where corticopontine fibers synapse. The tegmentum area contains cranial nerve nuclei (V, VI, VII, VIII), trapezoid body, medial lemniscus, parts of the reticular formation and the medial longitudinal fasciculus.

Pontine Control of Respiration

THOMAS E. DICK¹, MATHIAS DUTSCHMANN²,
KENDALL F. MORRIS³

¹Division of Pulmonary, Critical Care and Sleep Medicine/Department of Medicine, Case Western Reserve University, Cleveland, OH, USA

²Department of Neuro and Sensory Physiology, Georg August University of Göttingen, Göttingen, Germany

³Department of Molecular Pharmacology and Physiology Neuroscience, University of South Florida College of Medicine, Tampa, FL, USA

Synonyms

Pontine respiratory group; Pneumotaxic center; Ponto-medullary respiratory pattern generator

Definition

Pontine control of respiration involves the modulation of the timing and amplitude of the muscle activities that execute breathing, and airflow in and out of the lungs. Breathing is a vital function. Together with the cardiovascular system, breathing supplies oxygen to maintain general metabolism and is thus essential for bodily function. Importantly, breathing is also integrated with other mammalian behaviors like vocalizing, swallowing, coughing, and sniffing. Thus, breathing interacts with the environment not only in terms of inhaling and exhaling gas but also in terms of communication, food consumption, airway protection, and odor detection. The pons modulates breathing not only for gas exchange but also in these different behaviors.

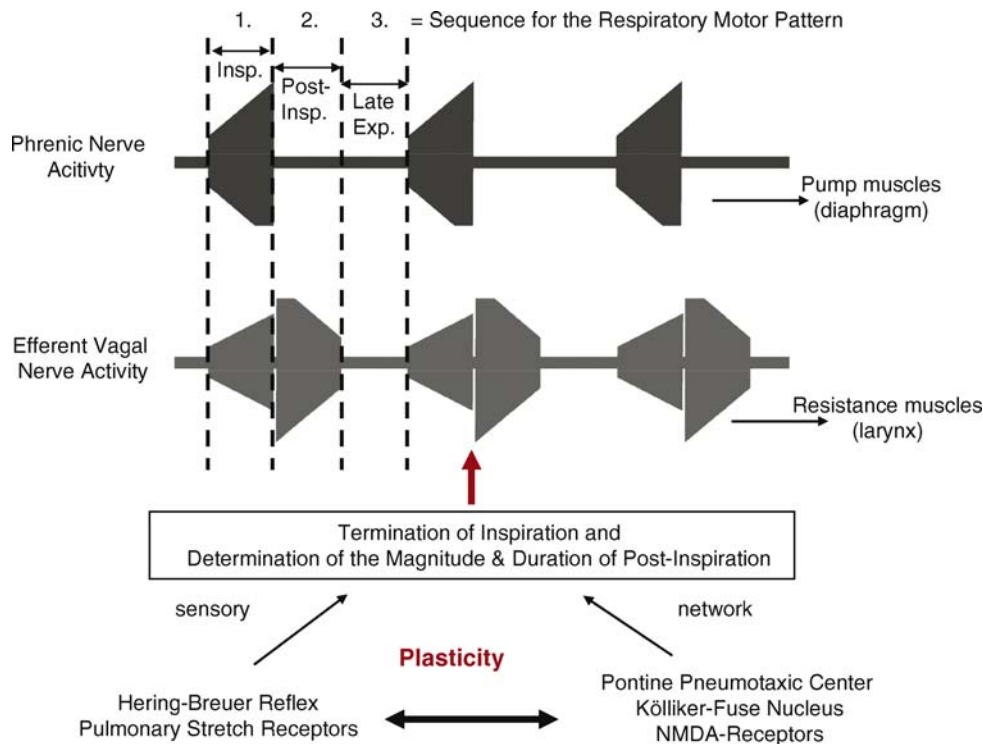
Characteristics

Pontine Influences on the Respiratory Motor Pattern

Breathing in mammals is controlled by a distributed network of neurons located bilaterally in columns of neurons that extend from the ventrolateral medulla to the parabrachial/Kölliker-Fuse complex in the rostral dorsolateral pons [1]. The medulla generates the primary respiratory rhythm and motor pattern, while the pontine nuclei exert strong modulatory influences on the respiratory frequency and shape of the respiratory motor pattern.

The respiratory motor pattern is defined by a sequence of bursts of different motor activities that are commonly divided into three major phases: (i) inspiration, (ii) postinspiration (early expiration or passive expiration), and (iii) late expiration (active expiration) (Fig. 1).

During the inspiratory and late expiratory phases, spinal motoneurons receive excitatory drive to contract thoracic and abdominal striated muscles including the diaphragm, to pump air in and out of the lungs (Fig. 1). Complementary motor activities transmitted in the cranial nerves (glossopharyngeal (IX), vagal (X), and hypoglossal (XII) nerves) target muscles that modulate airway resistance. During the inspiratory phase, posterior cricoarytenoid muscles and laryngeal abductors decrease upper airway resistance by pulling the vocal chords apart, whereas during the postinspiratory phase, the thyroarytenoid muscles that act as adductors increase resistance by drawing the vocal chords together. Laryngeal adductor activity depends on the pons (Fig. 2). Even in resting breathing, activity of laryngeal adductors (as well as inactivity of the airway dilators) limits or “brakes” expiratory airflow to prevent ▶atelectasis especially in mammals with highly compliant chest walls. Thus, even though we separate pontine modulation of rhythm or timing from that of motor activity, these two variables are not independent. Pumping and resistance motor activities are associated with the phases of the respiratory cycle and



Pontine Control of Respiration. Figure 1 Schematic drawing illustrating the coordinated pattern of two representative motor activities critical in defining the breathing pattern – phrenic nerve activity (top) and efferent vagal nerve activity (bottom). In these recordings, the sequential phases of the respiratory cycle ((i) inspiration, (ii) postinspiration, (iii) late expiration) can be identified. Two convergent pathways, an afferent pathway mediating the Hering-Breuer reflex and a central pathway that requires the dl pons, control the termination of inspiration and the duration of the postinspiratory phase of the breathing cycle. Plasticity in the expression of the breathing pattern depends on the pons and results from interaction between afferent and network pathways.

are coordinated by synaptic interactions within circuits of the pontomedullary respiratory network.

Pontine and Vagal Afferent Interaction Influences Timing of the Pattern

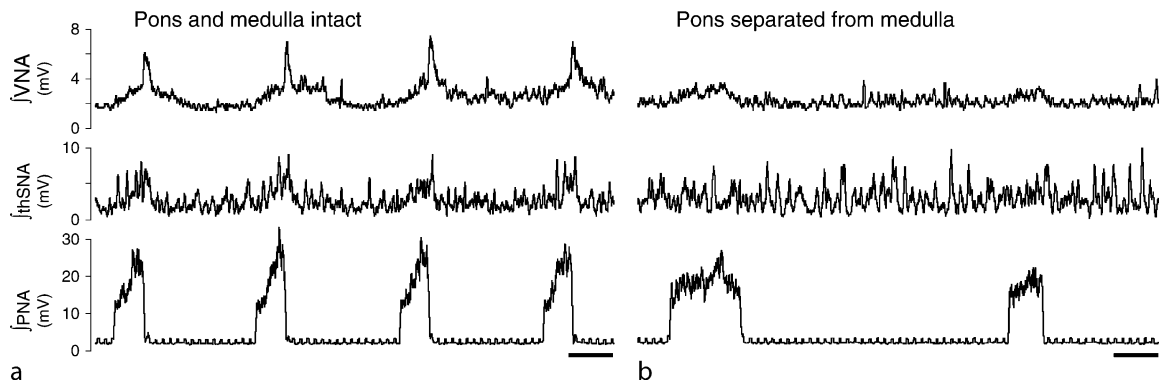
The importance of the pons in the neuronal control of breathing was established by Marckwald in 1888 [1]. He investigated breathing in rabbits and noted that after transecting both vagal nerves, respiratory rhythm became apneustic (►apneusis) after mid-pontine transection (compare phrenic nerve activity pattern before and after pontomedullary transection in Fig. 2). These studies complement those of Breuer, conducted in Hering's laboratory in 1868 [2]. They showed that lung inflation evokes a reflex that shortens inspiration and lengthens expiration and that this reflex, namely, the ►Hering-Breuer Reflex was vagally dependent and mediates the afferent input from pulmonary stretch receptors. An interpretation of Marckwald's work was that the pons acted like an "internal vagus" acting on the same medullary neurons that mediate the Hering Breuer reflex. Subsequent studies have supported this interpretation [3]. Stimulating the lateral pons evokes

phase switching, and recording neuronal activity in the dl pons shows that the magnitude and strength of its respiratory modulation increases in the absence of vagal input [4,5].

Interestingly, the Hering-Breuer reflex is of minor importance in the regulation of breathing in humans. However, breathing is not simply a stereotyped rhythmic activity that is controlled reflexly from the pulmonary stretch receptors of the lungs and chemoreceptors of the vasculature but rather a behavior whose function and control is incorporated into the context of other behaviors like vocalizing. Thus, the importance of the pons in respiratory control may be in determining breathing pattern in the context of behavior.

Expression of Plasticity in the Breathing Pattern Depends on the Pons

Activity-dependent plasticity (See Encyclopedia Article Respiratory Neuroplasticity by Morris and Bolser) of the breathing pattern is evident after brief (seconds to minutes) activation of afferent pathways whether they are mechanosensory (vagal afferent) [6] or chemosensory [7] pathways. Following stimulation, the breathing



Pontine Control of Respiration. Figure 2 Recordings of respiratory-modulated motor activities recorded from a vagus nerve (VNA, upper trace), phrenic nerve (PNA, lower trace), and thoracic sympathetic chain (thSNA), before (left) and after (right) pontomedullary transection. (a) With the pons connected to the medulla (recording from working heart brainstem preparation, see Encyclopedia Article Central Integration of Cardiovascular and Respiratory Activity Studied *In Situ* by Paton), breathing is regular as depicted by uniform pattern of activity from cycle-to-cycle. Specifically, VNA, which has some inspiratory activity increases sharply in the postinspiratory phase immediately after inspiration ceases when PNA burst ends. Sympathorespiratory coupling is evident in the inspiratory modulation of thSNA. (b) After pontomedullary transection, the respiratory rhythm as well as motor activity is irregular and disrupted, in particular, nonuniform durations of respiratory phases and no postinspiratory activity in the vagal motor nerve (Bar 1s).

pattern does not return immediately to baseline even though the controlled physiological variables such as blood gases have returned to baseline. Instead, the pattern gradually returns to baseline and this depends on the lateral pons because if input from the lateral pons is blocked, then the breathing pattern returns to baseline immediately. The pons may be acting directly on the pattern generator, particularly postinspiratory medullary neurons and may be acting through its ability to gate or regulate the incorporation of afferent information by the medulla [6]. The regulation of sensory input is a common way that behaviors override reflex control.

Anatomical studies indicate that the lateral pons and nuclei of the solitary tract (nuclei of the medulla (NTS) that receive mechano- and chemo-sensory input) are connected reciprocally (Fig. 1 – horizontal two-headed arrow at the bottom). Sensory information is transmitted to the Kölliker-Fuse nucleus and, in turn, the Kölliker-Fuse nucleus “gates” or modulates the efficacy of afferent input in the NTS; in particular, activity of the Kölliker-Fuse nucleus can suppress sensory input in NTS [8]. However, the precise synaptic interactions between NTS and Kölliker-Fuse nucleus still need to be elucidated.

The Role of the Pons in Respiratory Pattern Dysfunction

The respiratory pattern is highly variable in a mouse model for the Rett syndrome, which is a neurodevelopmental disease with severe respiratory disorders and lack of vocalization. This respiratory disturbance is associated with impairment of pontine and vagal

modulation of postinspiratory activity [9]. These data suggest that disturbance of the postinspiratory gating mechanisms causes severe respiratory disorders and that the pons has influence over variability, especially for other behaviors like vocalization.

Future Directions

Presently, while we know much about reflex control of the breathing and blood pressure both of which are controlled by pontomedullary networks, we know very little about the factors that integrate their control. This is especially true of those intrinsic to the brainstem. For instance, sympathorespiratory coupling is at least partially dependent on the pons (Fig. 2). Thus, the pons acts to coordinate the cardiorespiratory system to maintain homeostasis and oxygenation of vital organs including the CNS.

Oscillations (0.1 Hz) that are expressed in the blood pressure as ►Mayer Waves can influence the breathing pattern. Mayer Waves are thought to be related to baroreceptor reflex control of blood pressure. Preliminary analysis of pontine neuronal spike trains recorded continuously before and after vagal nerve transection suggests that in addition to the respiratory rhythm, a slow rhythm (~0.1 Hz) is also expressed by respiratory-modulated pontine activity. In some cases, this rhythm, which is normally masked, is strong enough that the respiratory rhythm itself becomes synchronized with it after vagotomy. The 0.1-Hz rhythm may be synchronized with Mayer Waves. In experiments in dogs, Mayer waves and the respiratory modulation of blood pressure, ►Traube-Hering waves,

were found to synchronize after vagotomy [10]. Additional preliminary analysis suggests that many pontine neurons that have respiratory modulation are also modulated with the blood pressure pulse of the cardiac cycle. These lines of evidence may indicate that individual pontine neurons are arranged in networks that help coordinate the intertwined control of breathing and perfusion. However, a great deal of work remains to elucidate the mechanisms of that coordination.

References

1. Alheid GF, Milsom WK, McCrimmon DR (2004) Pontine influences on breathing: an overview. *Respir Physiol Neurobiol* 143:105–114
2. Ullmann E (1970) About Hering and Breuer. In: Porter R (ed) *Breathing: Hering-Breuer centenary symposium*. London, Churchill, pp 3–15
3. Cohen MI, Wang SC (1959) Respiratory neuronal activity in pons of cat. *J Neurophysiol* 22:33–50
4. Feldman JL, Gautier H (1976) Interaction of pulmonary afferents and pneumotaxic center in control of respiratory pattern in cats. *J Neurophysiol* 39:31–44
5. St John WM (1987) Influence of pulmonary inflations on discharge of pontile respiratory neurons. *J Appl Physiol* 63:2231–2239
6. Siniaia MS, Young DL, Poon CS (2000) Habituation and desensitization of the Hering-Breuer reflex in rat. *J Physiol London* 523:479–491
7. Dick TE, Coles SK (2000) Ventrolateral pons mediates short-term depression of respiratory frequency after brief hypoxia. *Respir Physiol* 121:87–100
8. Dutschmann M, Morschel M, Kron M, Herbert H (2004) Development of adaptive behaviour of the respiratory network: implications for the pontine Kölliker-Fuse nucleus. *Respir Physiol Neurobiol* 143:155–165
9. Stettner GM, Huppke P, Brendel C, Richter DW, Gartner J, Dutschmann M (2007) Breathing dysfunctions associated with impaired control of postinspiratory activity in *Mecp2*^{-/-} knockout mice. *J Physiol (London)* 579: 863–876
10. Cherniack NS, Edelman NH, Fishman AP (1969) Pattern of discharge of respiratory neurons during systemic vasomotor waves. *Am J Physiol* 217:1375–1383

Pontine-Geniculate-Occipital (PGO) Waves

Definition

Bursts of excitation that arise in the brainstem and are subsequently detected in the visual thalamus and visual cortex.

► Sleep States

Pontine Micturition Center (PMC)

Definition

The PMC mediates spino-bulbo-spinal reflexes activated by sacral afferent neurons from the urinary bladder that are involved in micturition and continence of the urinary bladder. It consists of the medial PMC (Barrington's nucleus) which triggers micturition (contraction of the detrusor vesicae and relaxation of the external vesical sphincter) and the lateral PMC which maintains continence (inhibition of mechanisms leading to micturition, activation of the external vesical sphincter).

► Autonomic Reflexes

► Micturition

Pontine Nuclei

Definition

A group of neuronal populations located in the pons region of the hindbrain. They are the major source of the mossy fiber input to the cerebellar cortex in birds and mammals. They receive their input from the spinal cord, the striatum of the forebrain, and the tectum of the midbrain.

► Evolution of the Cerebellum

Pontine Respiratory Group

► Pontine Control of Respiration

Pontine Wave (P-Wave)

Definition

REM sleep-associated phasic field potential recorded in the pons. Lasting for 75–150 ms, the P-wave appears during REM sleep as clusters containing a variable number of waves (3–5 waves/burst) or a singlet with

amplitudes from 100 to 150 μV and a frequency range of 30–60 spikes/min. P-wave is the pontine component of ponto-geniculo-occipital (PGO) wave. The P-wave is generated by the phasic activation of a group of glutamatergic cells in the pons. The P-wave is critically involved in the reactivation of both the hippocampus and amygdala to reprocess cognitive information and to form memory traces in the cortex.

► Sleep

Pontocerebellum

Definition

The hemispheres belong to the phylogenetic young neocerebellum and receive their afferences via the moss fibers of the pontocerebellar tract from the pontine nuclei. Therefore, one also likes to summarize all hemispheric sections to the so-called pontocerebellum.

► Cerebellum

Pontomedullary Respiratory Pattern Generator

► Pontine Control of Respiration

Ponto-Pontine Long-Lead Burst Neurons

CHARLES SCUDDER
Portland, OR, USA

Definition

Ponto-pontine neurons, in general, are neurons that have both their somata and terminal fields in the pontine reticular formation. Ponto-pontine ►long-lead burst neurons (►burst cells – long lead (LLBNs)) (PP-LLBNs) are ponto-pontine neurons that exhibit long-lead burst discharges during ►saccades. Although

some PP-LLBNs have been experimentally identified, those having the well defined functions expected from theory remain hypothetical at this point.

Characteristics

Higher Order Processes

Based on experimental studies of the saccadic system and on models of the saccadic system that incorporate these experimental results, PP-LLBNs are needed to relay signals from higher saccadic command centers to the ►saccadic burst generator. These command centers consist of the deep and intermediate layers of the ►superior colliculus with weaker projections from ►frontal eye fields (FEF). The superior colliculus, in turn, coalesces saccade-related information from the frontal eye fields, the ►supplementary eye fields (SEF), the ►lateral intraparietal area (LIP), and the ►substantia nigra and issues the principal saccadic command. Neurons in the FEF and superior colliculus both have long-lead discharge patterns, and provide the long-lead signal to the PP-LLBNs.

Lower Level Processes

PP-LLBNs are thought to convey the saccadic command to the ►excitatory burst neurons (EBNs), ►inhibitory burst neurons (IBNs), and ►omnipause neurons (OPNs) of the saccadic burst generator. There are at least two, and possibly three, populations of PP-LLBNs that project to these neurons.

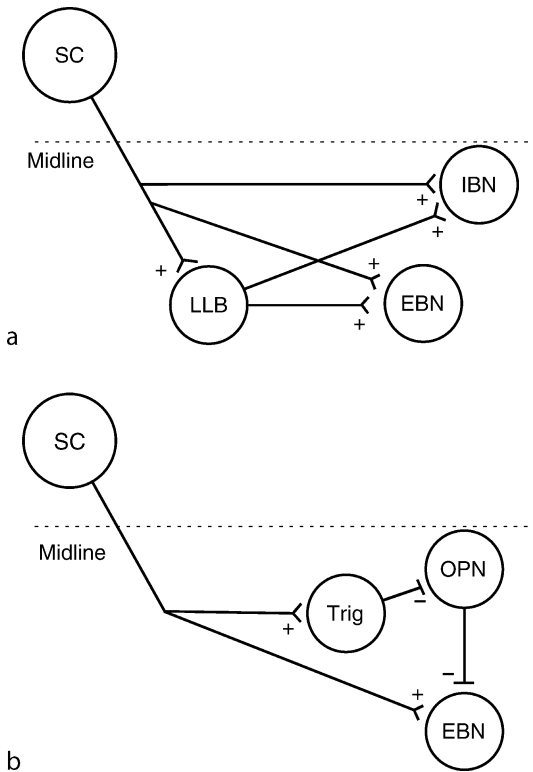
Parts of the Ponto-Pontine LLBN System

Excitatory Relay PP-LLBNs

The generation of saccades requires a powerful excitatory input to the EBNs and IBNs. This excitation could be provided by a direct input from the superior colliculus, or by way of PP-LLBNs intercalated between the superior colliculus and the burst neurons [1]. Experimental data supports both possibilities. In the monkey, the superior colliculus does not project directly to EBNs, but does project to long-lead burst neurons (LLBNs) located in the pontine reticular formation [2]. PP-LLBNs do project to the region containing EBNs (see below), and must connect with EBNs, or else EBNs would have no suitable input. In the cat, a direct connection from the superior colliculus to EBNs has been demonstrated, but a parallel indirect pathway exists that most likely involves PP-LLBNs [3–5]. Similarly, cat IBNs receive direct and indirect input from the superior colliculus [3–6]. This set of connections is illustrated in Fig. 1a.

Inhibitory Trigger Neurons

Another population of PP-LLBNs, called ►trigger neurons, is needed to initiate the saccade. Activity in the superior colliculus activates the trigger neurons, which inhibit the tonically active OPNs. The pause



Ponto-Pontine Long-Lead Burst Neurons.

Figure 1 A portion of the wiring of the saccadic burst generator showing the connections of two pools of PP-LLBNs. (A) Relay PP-LLBNs (LLB) convey the output of the superior colliculus (SC) to the premotor burst neurons; excitatory burst neurons (EBN) and inhibitory burst neurons (IBN). The connections are all excitatory (+). The SC also has direct connections to the EBNs and IBNs in the cat. (B) Inhibitory PP-LLBNs (Trig) convey the output of the SC to omnipause neurons (OPN) in order to silence them and trigger the start of the saccade. Inhibition is signified by the “-” sign. A more complete diagram showing the relation of these components to the whole burst generator is presented in the brainstem burst generator section.

in OPN activity disinhibits the burst neurons (see ►[Brainstem burst generator](#)) and allows them to discharge. The inhibitory trigger neurons intercalated between the superior colliculus and OPNs ([Fig. 1b](#)) are needed to accomplish the inhibition of the OPNs, because the efferents of the superior colliculus are excitatory. In agreement, microstimulation of the superior colliculus leads to inhibitory potentials in OPNs at disynaptic latencies, and intracellular recordings from OPNs in alert cats reveals a pre-saccadic phase of inhibition that is possibly mediated by trigger LLBNs [6–8]. Microstimulation in the ►[paramedian pontine reticular formation \(PPRF\)](#) where LLBN somata are prevalent produces inhibition in OPNs [6].

Identified PP-LLBNs

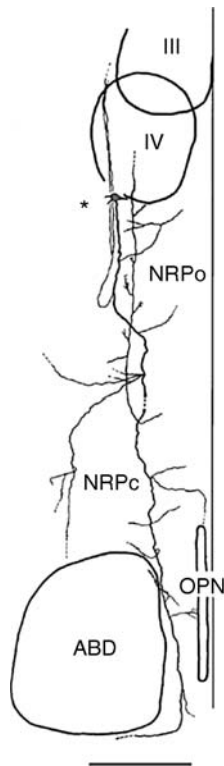
Definitive anatomical and physiological evidence for the existence of PP-LLBNs consists of four PP-LLBNs revealed using the intraaxonal labeling technique [9]. The small sample size probably does not reflect a paucity of PP-LLBNs, but rather the difficulty and biases of the intraaxonal technique. All four neurons are anatomically different, but nonetheless innervate many of the same parts of the reticular formation. The diversity of these neurons, together with various fragments of incompletely labeled neurons, shows that there may be a large variety of PP-LLBNs.

Somata of three neurons were located in the rostral PPRF (NRPo) caudal and ventral to the trochlear nucleus. The soma of the fourth was located at the mid PPRF just rostral to the EBN area. Axons of all four descended in the PPRF, and all four axons gave off one or two branches that ascended to, and sometimes terminated in, the ipsilateral mesencephalic reticular formation (cf. [Fig. 2](#)). Most (3/4) had branches that terminated in ipsilateral NRPo, and all had branches that terminated in the part of ipsilateral caudal PPRF (NRPC) where EBNs are located. They also all had branches that innervated ►[raphe interpositus](#) (the locus of OPNs) or the immediately adjacent region containing OPN dendrites. Less frequent targets included ►[NRTp](#), raphe pontis, the contralateral PPRF, the IBN area, and ►[nucleus reticularis gigantocellularis](#) (one origin of reticulospinal pathways). One axon could be followed well into the medulla and may have been headed for the spinal cord.

As with other LLBNs, PP-LLBNs were mostly silent during fixation, and gradually began firing on average 44–107 ms preceding the start of ►[ipsiversive](#) saccades. Firing rate peaked just before the saccade start, and ended just before saccade end. The spatial properties of their discharges were as varied as their anatomy. Two were ordinary ►[vectorial burst neurons](#) (discharging only for saccades to a small circumscribed region of visual space – the ►[movement field](#)), one was a vectorial burst neuron with an unusually wide movement field, and the fourth was a ►[directional burst neuron](#) that discharged for all saccades into the ipsiversive visual space.

Pathology

PP-LLBNs and their axonal and terminal processes are intermixed in the PPRF with a multitude of eye-movement related and other neurons. Experimental and natural lesions of the region that contains PP-LLBNs necessarily destroy these other neurons as well, so deficits cannot be attributed to one population alone. Lesions of the PPRF can impair most types of horizontal eye movements; ►[VOR](#), ►[smooth pursuit](#), ►[optokinetic nystagmus](#), and saccades [10]. Many of these deficits can be traced to damage of fibers that traverse the PPRF, but



Ponto-Pontine Long-Lead Burst Neurons.

Figure 2 Camera lucida drawing of a PP-LLBN in the left side of the pontine reticular formation reconstructed in a horizontal plane. The soma (*) is ventral and immediately caudal to the trochlear nucleus (IV), and the axon descends through the nucleus reticularis pontis oralis (NRPo) and ►nucleus reticularis pontis caudalis (NRPc). Terminal arborizations innervate these structures, including the part of NRPc containing excitatory burst neurons. Other branches terminate just lateral to the omnipause neurons (OPN). ABD = abducens nucleus, III = oculomotor nucleus. Dashed lines indicate fading of the label. Calibration bar is 1 mm.

deficits in saccades are surely the result of destruction of the saccade-related neurons in the PPRF. Small unilateral lesions cause a slowing and shortening of ipsiversive saccades. Larger unilateral lesions eliminate all ipsiversive saccades, and large bilateral lesions eliminate all horizontal saccades. Large caudal lesions that involve the OPNs also affect vertical saccades.

References

1. Hepp K, Henn V (1983) Spatio-temporal recoding of rapid eye movement signals in the monkey paramedian pontine reticular formation (PPRF). *Exp Brain Res* 52:105–120
2. Keller EL, McPeck RM, Salz T (2000) Evidence against direct connections to PPRF EBNs from SC in the monkey. *J Neurophysiol* 84:1303–1313

3. Chimoto S, Iwamoto Y, Shimazu H, Yoshida K (1996) Monosynaptic activation of medium-lead burst neurons from the superior colliculus in the alert cat. *J Neurophysiol* 75:2658–2661
4. Grantyn AA, Grantyn R (1976) Synaptic actions of tectofugal pathways on abducens motoneurons in the cat. *Brain Res* 105:269–285
5. Izawa Y, Sugiuchi Y, Shinoda Y (1999) Neural organization from the superior colliculus to motoneurons in the horizontal oculomotor system of the cat. *J Neurophysiol* 81:2597–2611
6. Kamogawa H, Ohki Y, Shimazu H, Suzuki I, Yamashita M (1996) Inhibitory input to pause neurons from pontine burst neuron area in the cat. *Neurosci Lett* 203:163–166
7. Yoshida K, Iwamoto Y, Chimoto S, Shimazu H (1999) Saccade-related inhibitory input to pontine omnipause neurons: An intracellular study in alert cats. *J Neurophysiol* 82:1198–1208
8. Yoshida K, Iwamoto Y, Chimoto S, Shimazu H (2001) Disynaptic inhibition of omnipause neurons following electrical stimulation of the superior colliculus in alert cats. *J Neurophysiol* 85:2639–2642
9. Scudder CA, Moschovakis AK, Karabelas AB, Highstein SM (1996) Anatomy and physiology of saccadic long-lead burst neurons recorded in the alert squirrel monkey. II. Pontine neurons. *J Neurophysiol* 76:353–370
10. Leigh RJ, Zee DS (1999) The neurobiology of eye movements. Oxford University Press, New York

Population Code

Synonyms

Also Ensemble Code

Definition

Population code (also ensemble code) denotes a code by which neural information is encoded in the spatiotemporal activity patterns of many neurons.

►Sensory Systems

Population Vector

Definition

An algorithm for estimating a vectorial quantity encoded by the spiking activity of a neuronal population given the response characteristics of each individual neuron to different values of that vectorial quantity (tuning curve). Originally proposed for decoding the

hand movement direction from the firing rate of a population of directionally tuned neurons in the motor cortex of macaque monkeys. To compute the population vector in a specific condition (e.g. a specific movement direction), given the tuning curve of each cell (determined from the cell's response in several conditions) and the response vector associated to its maximum (e.g. the cell's preferred direction), all the response vectors, weighted by the cell firing rates in that specific condition, are summed together.

► Reaching Movements

Pore Loop

Definition

The pore loop represents a short amino acid sequence that forms the ion permeation pathway of tetrameric cation channels. In voltage-gated cation channels this domain is localized between the S5 and S6 segment.

The X-ray structure of the pore loop has been resolved in the bacterial KcsA channel. The domain consists of an α helical portion (the pore helix) and an uncoiled strand of 4–5 amino acid residues (the selectivity filter) forming the narrowest part of the pore.

► Cyclic Nucleotide-Regulated Cation Channels

Pore-loop Channels

Definition

Pore-loop channels all bear an extracellular, re-entrant loop, which provides a highly selective aqueous pore for particular ions. All pore-loop channels are structural derivatives of inward rectifying potassium (K^+) channels, and are the largest class of channels within the ion channel family. Pore loop channels include the voltage-gated channels, including the potassium, calcium (Ca^{2+}) and sodium (Na^+)-selective channels, the inward rectifying and two pore potassium channels and the glutamate receptors.

- Calcium Channels – an Overview
- Ion Channels from Development to Disease
- Glutamate Receptors
- Neuronal Potassium Channels
- Sodium Channels

Porphyrins

► Photopigments

Position Sense

Definition

The ability to detect the position of joints of the body. It is tested clinically as part of assessments of proprioception.

- Joint position sense
- Proprioception and Orthopedics
- Proprioception Role of Joint Receptors

Positional Alcohol Nystagmus

Definition

Nystagmus resulting from alcohol intoxication. The nystagmus is due to the passage of alcohol into the cupula of each of the semicircular canals, which renders them lighter than the surrounding endolymph. The semicircular canals then respond to changes in head position resulting in positional nystagmus. A second phase is noted when alcohol diffuses from the cupula and into the endolymph. An oppositely directed positional nystagmus is then noted.

- Disorders of the Vestibular Periphery
- Semicircular Canals

Positional Cloning

Definition

Positional cloning is a technique used to identify genes, either associated with disease or with a mutant in an animal model, based on their location on a chromosome.

Position-Vestibular-Pause Neurons

KATHLEEN E. CULLEN

Department of Physiology, Aerospace Medical Research Unit, McGill University, Montreal, QC, Canada

Definition

Traditionally, the vestibulo-ocular reflex (VOR) is considered to be a stereotyped reflex that effectively stabilizes gaze by moving the eye in the opposite direction to concurrent head motion. The three neuron arc responsible for mediating the VOR was first described by Lorente de No' in 1933. This pathway consists of projections from vestibular afferents to interneurons in the vestibular nuclei, which in turn project to extraocular motoneurons. The simplicity of this three neuron arc is reflected in the fast response time of the VOR; compensatory eye movements lag head movements by only 5–6 ms in the primate [1]. Horizontal and vertical position-vestibular-pause (PVP) neurons are thought to constitute most of the intermediate leg of the direct pathway that mediate the VORs, which are evoked by yaw and pitch rotations, respectively. As the response of horizontal PVP neurons have been more extensively investigated in alert animals, they are the focus of this essay.

The results of recent investigations have changed our view of the VOR. In particular, neurophysiological recordings from PVP neurons provide firm evidence that the VOR is not a hard wired reflex, as had been commonly assumed. This essay first describes the responses of PVP neurons during field standard tests including passive whole body rotations and eye-movements in head-restrained monkeys. Next, the results of studies that have characterized PVP neurons during (i) redirections of gaze that are produced by coordinated eye-head movements, and (ii) gaze stabilization while viewing near versus far targets during head movements, are summarized. These findings are considered in relation to the sensory-motor transformations needed to guide behavior in a manner consistent with current gaze strategies.

Characteristics

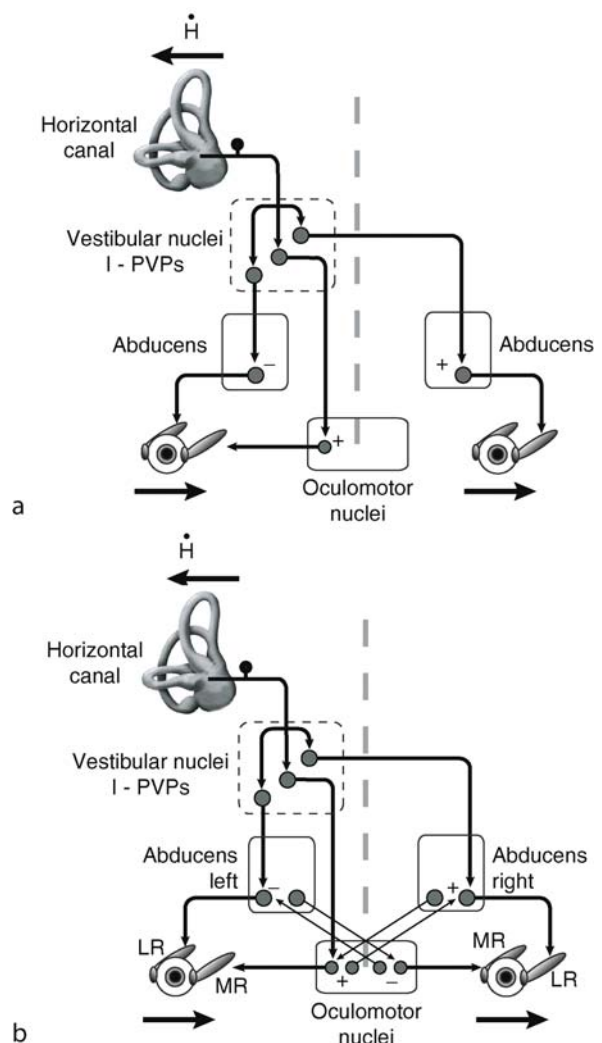
Response During Standard Head-Restrained Rotations and Eye Movements

Type I Neurons

► Type I position-vestibular-pause (PVP) neuron constitute most of the intermediate leg of the direct pathway that produces the horizontal VOR (reviewed in [2]). The majority of type I PVP neurons are located in the rostral medial vestibular nucleus, and send an excitatory projection to the motoneurons of the (i) contralateral

► abducens nucleus, or (ii) ipsilateral medial rectus subdivision of the ► oculomotor nucleus (Fig. 1a). A minority send inhibitory projections to the motoneurons of the ipsilateral abducens nucleus. Within the abducens nucleus, motoneurons project directly to the ipsilateral lateral rectus muscle (LR), while a separate class of neurons (internuclear neurons) project to the contralateral oculomotor nucleus, which projects to the medial rectus muscle (MR; Fig. 1b). During horizontal eye movements, the effective force moving the eye is generated by the sum of the forces of the LR and MR.

Type I PVP neurons derive their name from the signals they carry during head-restrained rotation and eye movement paradigms. Their firing rates increase with contralaterally directed eye position; they are sensitive to

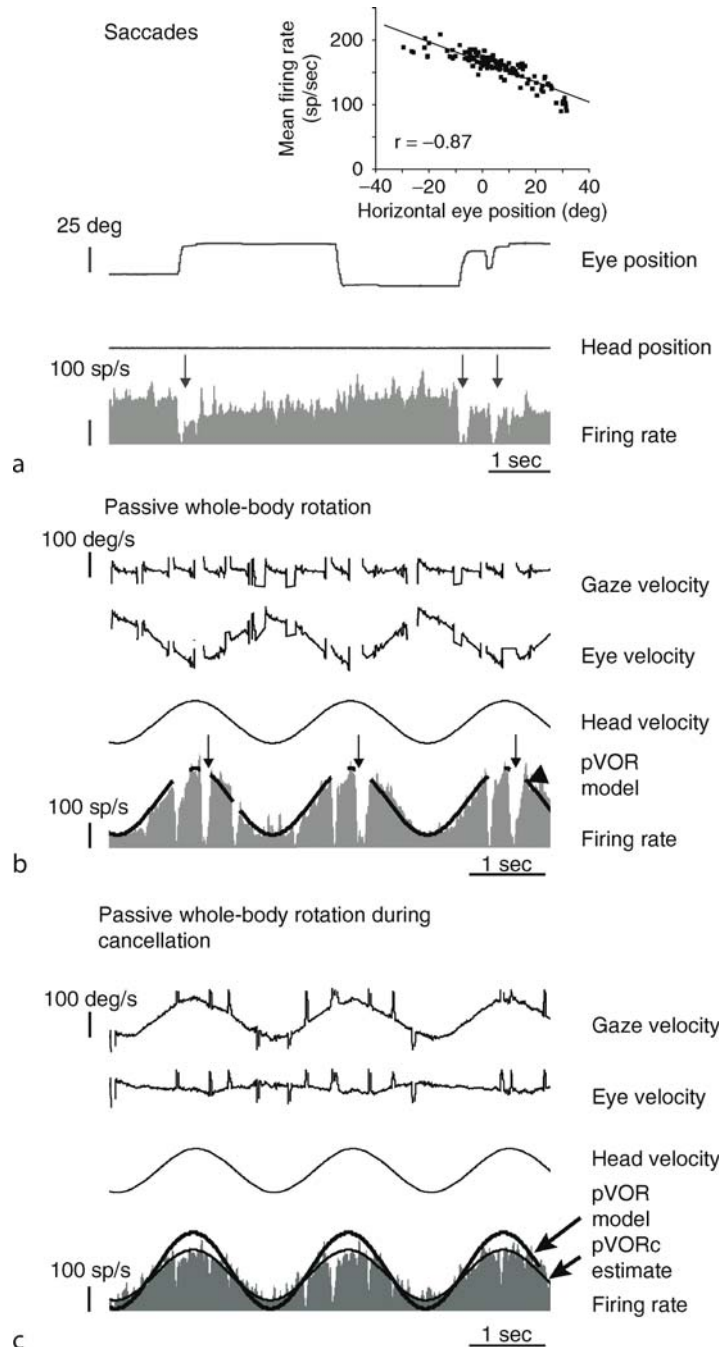


Position-Vestibular-Pause Neurons.

Figure 1 (a) Direct VOR pathway; rotation of the head to the left generates right eye movements. (b) Connections between the abducens and oculomotor nuclei.

ipsilaterally directed head velocity during vestibular stimulation (i.e. a type I response); and their discharges cease (pause) for ipsilaterally directed saccades and vestibular quick phases. In addition, these neurons show modulation for contralaterally directed eye movements during ►smooth pursuit tracking. The activity of a typical

PVP neuron is illustrated in Figs. 2a–c. The neuron's mean firing rate is linearly related to eye position during periods of steady ocular fixation (Fig. 2a). During sinusoidal passive whole-body rotation in the dark at 0.5 Hz, neuronal modulation leads ipsilateral head rotation by about 10–20° (Fig. 2b), and the neuron pauses or stops



Position-Vestibular-Pause Neurons. Figure 2 Activity of an example type I PVP neuron in the head-restrained condition. (a) Responses are correlated with horizontal eye position during periods of steady fixation. (b, c) Responses to passive whole-body rotation during (b) the VOR in the dark (pVOR), and (c) cancellation of the VOR by fixation of a target that moves with head (pVORc).

firing during ipsilaterally directed vestibular quick phases (Fig. 2b, downward arrows). The behavior of PVP neurons during the compensatory slow phase VOR evoked by passive rotation can be well described by the equation:

$$fr = a + kE + gH' + cH''$$

where fr = neuronal firing rate, a is the resting discharge, E is eye position, k is the eye position sensitivity of the neuron during ocular fixation, H' and H'' are head velocity and acceleration, respectively, and g and c are neuronal sensitivities to head velocity and acceleration, respectively.

In order to dissociate the vestibular-related modulation of PVP neurons from their eye-movement related responses, vestibular physiologists have traditionally utilized a paradigm in which the monkey “cancels” its VOR by tracking a target that moves with the head. The resulting vestibular stimulation does not lead to eye motion in the opposite direction to the head motion, since trained subjects can accurately follow the target at frequencies <1.5 Hz. Type I PVP neurons respond robustly to ipsilaterally directed head velocity in this condition, but show a 30% decrease in modulation as compared to VOR in the dark (Fig. 2c [3,4]). This reduction in head-velocity sensitivity occurs at latencies that are too short to be mediated by smooth pursuit pathways (see Fig. [3]), and supports the idea that there is a parametric adjustment of the gain of the direct VOR pathway while the VOR is voluntarily suppressed. Signals carried to the extraocular motoneurons by other premotor inputs help offset the residual modulation of PVP neurons, so that the eye remains immobile (see essay on VOR suppression).

Type II Neurons

During head-restrained rotations and eye movements, the head and eye movement sensitivities of type II PVP neurons are opposite to those of type I PVP neurons; firing rates increase in response to contralaterally-directed head rotation and ipsilaterally directed eye position and velocity. Otherwise, the firing pattern of these two types of neurons is very similar. The projections of type II PVP neurons are not known, however it is thought that they support inhibitory commissural pathways between vestibular nuclei [2] and that they contribute to the weak three neuron arc that, in part, mediates the translational VOR (see section on “Translational VOR” below). In addition, it is likely that the inhibitory inputs from type II PVP neurons contribute to the pause-behavior of type I PVP neurons during ipsilaterally directed saccades, vestibular quick phases, and ►gaze shifts. This proposal is consistent with known interconnections between the brainstem saccade generator and the vestibular nuclei [5].

PVP Neuron Modulation: Voluntary Head Movements

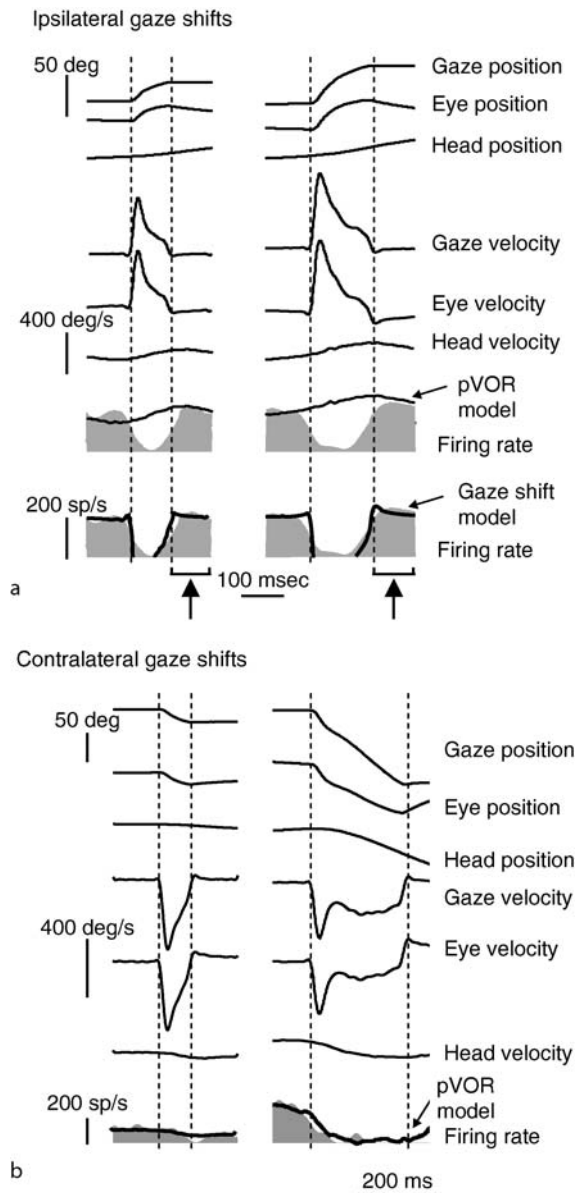
Recent work has shown that PVP neurons process vestibular information in a manner that depends principally on the subject’s current gaze strategy, rather than whether the head movement was actively generated or passively applied. As described below, the head velocity signal carried by the direct VOR pathway is reduced when the behavioral goal is to redirect the visual axis of gaze. In contrast, PVP neurons robustly encode head velocity signals when the behavioral goal is to stabilize the visual axis of gaze relative to space, regardless of whether head movement is actively or passively generated.

Gaze Redirection

There is much accumulated evidence from studies in head-restrained monkeys to indicate that both type I and II PVP neurons differentially encode head-velocity during gaze redirection versus gaze stabilization. First, as described above, while PVP neurons encode head velocity during the compensatory slow phase component of the VOR evoked by passive whole-body rotation, they pause or significantly decrease their firing during vestibular quick phases where gaze is redirected. In addition, PVP neuron responses are significantly attenuated, as compared to passive rotation in the dark, when the VOR is suppressed during passive whole-body rotation by tracking a target that moves with the head. In this latter condition, the goal is to redirect the axis of gaze relative to space rather than stabilize gaze [3,4].

It is useful to suppress PVP transmission in each of the above circumstances, since eye movement commands generated by the direct VOR pathways would function to drive the eye in the opposite direction to the intended change in gaze. An analogous argument can be made for situations in which the axis of gaze is voluntarily redirected, a combination of eye and head movements. In order to rapidly redirect the visual axis towards a target of interest, primates commonly generate coordinated eye-head movements, termed gaze shifts. Similarly, coordinated smooth head and eye movements (i.e. ►gaze pursuit) are frequently generated in order to track moving targets. Attenuating the modulation of the direct VOR pathways (i.e. type I PVP neurons) during either gaze shifts or gaze pursuit would also be behaviorally advantageous.

Indeed, during rapid orienting gaze shifts, the head-velocity related signals carried by type I PVP neurons are dramatically reduced [2,5,6]. As shown in Fig. 3a, neuronal responses to head velocity during ipsilateral gaze shifts are consistently attenuated relative to passive whole-body rotation in the dark (i.e. during the VOR, Fig. 2c). As a result, a model based on a neuron’s response during passive rotation (Fig. 3a; heavy line: pVOR model) will systematically over-predict



Position-Vestibular-Pause Neurons. Figure 3 The activity of a type I PVP neuron during and following ipsilaterally (a) and contralaterally (b) directed gaze shifts. Arrows indicate the post gaze shift intervals in (a).

its discharge during gaze shifts. Moreover, neuronal modulation is increasingly attenuated for larger amplitude gaze shifts reaching 70% attenuation for gaze shifts $>60^\circ$ [2,5]. Type I PVP neurons also contribute little to the generation of the VOR during large contralaterally directed gaze shifts, since they are typically driven into inhibitory cut-off (Fig. 3b). Overall, the amplitude-dependent attenuation of the discharge of these neurons is consistent with the results of behavioral studies demonstrating that the VOR is more strongly

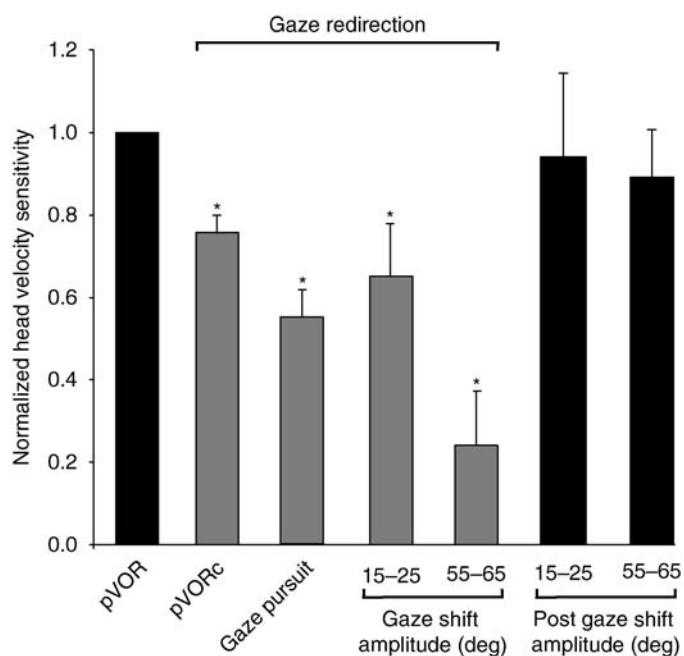
suppressed during large than during small gaze shifts (see essay on “VOR suppression”). Similar results have been obtained from characterizations of type II PVP neurons [2].

The head-velocity related modulation of PVP neurons is also reduced when gaze is redirected to follow a moving target by means of coordinated eye-head pursuit. Responses to the voluntary head movements that are generated during eye-head pursuit are attenuated by approximately 30% compared to responses to passive whole-body rotation. Thus, the attenuation observed during eye-head pursuit is comparable to that observed when the VOR is suppressed by fixating a target that moves with the head (Fig. 2c), as well as that observed during small rapid gaze shifts ($<25^\circ$). The histogram in Fig. 4 summarizes the head velocity-related signals that are carried by PVP neurons across different voluntary behaviors, and emphasizes the fact that transmission through the VOR pathways is attenuated during all behaviors that involve gaze redirections.

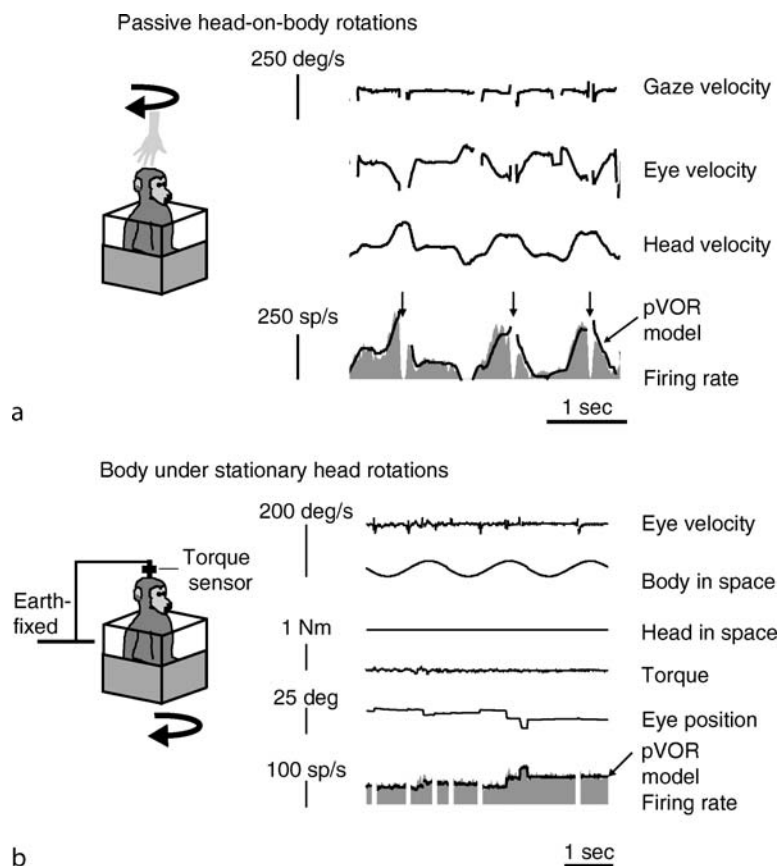
Gaze Stabilization

As described above, an intact VOR is not beneficial when the behavioral goal is to redirect gaze to a new target. In contrast, a fully functional VOR is clearly critical when the behavioral goal is to maintain stable gaze. Moreover, there have been reports that VOR performance is enhanced in response to active head rotations compared to passive whole-body rotations [1]. These findings have led to the suggestion that neck proprioceptive signals and/or a copy of the command to the neck motoneurons might function to augment transmission in the VOR pathways (i.e. PVP neurons) during active head movements.

Single unit recording experiments, however, indicate that neither neck proprioceptive nor neck motor efference copy signals augment the modulation of PVP neurons during active head-on-body movements. First, in rhesus monkeys, PVP neurons encode head movement in the same manner during passive head-on-body rotations and passive whole-body rotations (Fig. 5a; [1,2]). In addition, PVP neurons are not modulated in response to passive rotation of the body under a stationary head (Fig. 5b [2]). Thus, the passive activation of neck proprioceptors does not significantly alter the sensorimotor transformations carried out at the level of the direct VOR pathways. Second, neuronal responses are comparable during passive whole-body rotations and active head movements that are produced during periods of stable gaze [2,5,6]. For example, as shown in Fig. 3a, immediately following a rapid orienting gaze shift, the head continues to move even after gaze has stabilized relative to space (intervals denoted by the arrows). During this interval, a neuron's activity can be predicted based on its response to



Position-Vestibular-Pause Neurons. Figure 4 Summary of type I PVP neuron discharge activity during passive and voluntary head motion. The (*) symbol denotes significant attenuation as compared to pVOR.



Position-Vestibular-Pause Neurons. Figure 5 (a) The head was passively rotated on a stationary body. (b) Neuronal responses are not modulated by passive stretching of neck proprioceptors produced by passively rotating the body under a stationary head.

passive whole body rotation (heavy line). Taken together, these results are consistent with accumulating evidence from behavioral studies showing that VOR performance is generally comparable during passive and active rotations of the head-on-body in primates [1].

Summary

Recent single unit experiments show that the head velocity signals carried by the direct VOR pathways are modulated in a manner that is consistent with the current behavioral goal. PVP neurons demonstrate robust head-velocity related modulation in response to self-generated and passively applied head rotations when gaze is stable. In contrast, when the behavioral goal is to redirect gaze relative to space, the head-velocity signals carried by PVP neurons are significantly reduced.

PVP Neuron Modulation: Near Versus Far Viewing During Rotations and Translations

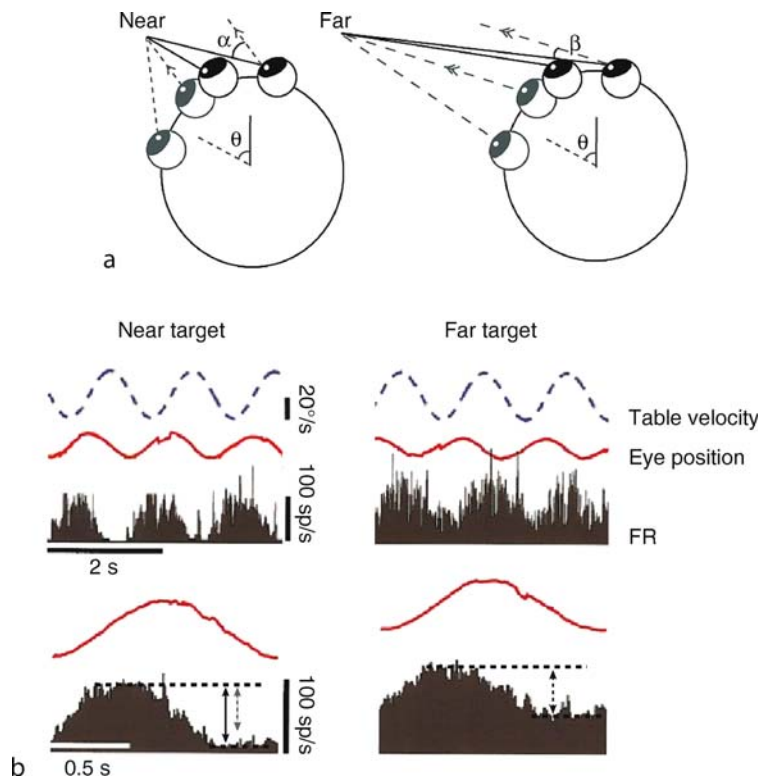
Angular VOR

A second situation where the VOR shows behaviorally-dependent modulation is during the fixation of near versus far earth-fixed targets. During head rotations, the eyes translate as well as rotate relative to space, since

they cannot both be perfectly aligned with the axis of rotation. Consequently, for the same amplitude of head rotation, a larger VOR gain is necessary to stabilize a near than a far earth-fixed target due to the differences in the translation of the target relative to the eyes (Fig. 6a). Differences in the responses of the type I PVP neurons that mediate the direct VOR pathways are consistent with these distance-related changes in VOR gain (Fig. 6b [7]).

Translational VOR

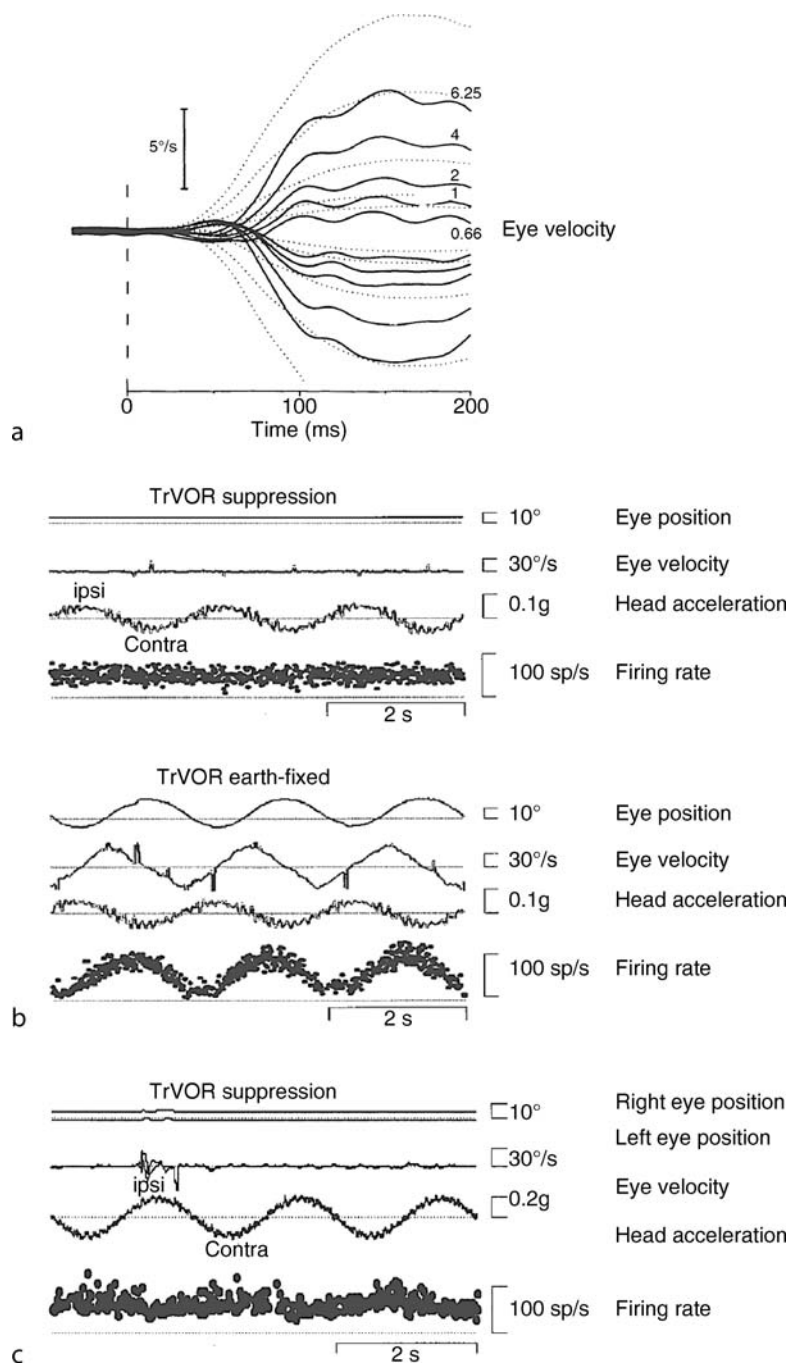
Recently, several investigations have specifically focused on the premotor pathways that generate the VOR in response to stimulation of the otoliths during translations (i.e. the translational VOR (TVOR); [8]). The latency of the TVOR is somewhat longer than that of the angular VOR; compensatory eye movements generally lag head movements by >10 ms in the primate. Although a direct disynaptic pathway has been shown to exist between the otoliths and the abducens nucleus, the longer latency of the TVOR suggests that it is primarily mediated by more complex polysynaptic pathways. During translation along the interaural axis, the gain of the horizontal TVOR response depends on



Position-Vestibular-Pause Neurons. Figure 6 (a) Effect of varying fixation target distance (D) on VOR gain for a fixed axis of rotation. (b) Responses of a type I PVP neuron when passive whole body rotation was applied while viewing a near (left panel) versus far (right panel) target.

the distance of the target being viewed (Fig. 7a). Moreover for translations along the nasal-occipital axis, the amplitude and sign of the eye movements evoked by the TVOR depend on gaze angle as well as viewing

distance. The latter finding is of particular interest, since it demonstrates that direction as well as the amplitude of the TVOR response is modified in a behaviorally-dependent manner.



Position-Vestibular-Pause Neurons. Figure 7 (a) Effect of varying fixation target distance on VOR gain during translation along the interaural axis. Continuous lines represent average eye velocity, while dotted lines indicate the ideal response that would be required for perfect gaze stability. (b, c) Responses of an example type I (b) and type II (c) PVP neuron during lateral translation.

Type I PVP neurons, which constitute the main interneuron in the direct angular VOR pathway, do not receive direct otolith inputs and thus do not contribute to the three neuron pathway that mediates the direct TVOR pathway. This is shown in Fig. 7b, where a typical neuron shows negligible response modulation during translation when the subject fixates a head-fixed target (TrVOR suppression; [8,9]). Comparison with Fig. 2c highlights the striking difference in response to type I PVP neurons during suppression of the TVOR and suppression of the angular VOR. However, when a subject fixates an earth-fixed target during translation (Fig. 7b, TrVOR earth fixed), neurons modulate in a manner that is consistent with their oculomotor-related response during smooth pursuit [9]. These results are in general agreement with previous studies that have compared responses during on and off-centered rotations [7,10]. Given that the type I PVP neurons show robust modulation during the TVOR, and that they project directly to the extraocular motoneurons (Fig. 1), it can be concluded that they contribute to the generation of the reflex via inputs from polysynaptic (but not direct) pathways.

In contrast, type II PVP neurons show slight response modulation during suppression of the VOR during translation (Fig. 7c), suggesting that these neurons contribute to the relatively weak ipsilaterally projecting three neuron arc that mediates the direct TVOR pathway. However, these neurons do not change their response amplitude for near versus far viewing during TVOR suppression [9]. Additional inputs, most likely transmitted via cerebellar/floccular pathways, appear to be necessary to modulate the TVOR as a function of gaze angle and viewing distance [7,8,9].

References

1. Cullen KE, Roy JE (2004) Signal processing in the vestibular system during active versus passive head movements. *J Neurophysiol* 91:1919–1933
2. Roy JE, Cullen KE (2002) Vestibuloocular reflex signal modulation during voluntary and passive head movements. *J Neurophysiol* 87:2337–2357
3. Cullen KE, McCrea RA (1993) Firing behavior of brain stem neurons during voluntary cancellation of the horizontal vestibuloocular reflex. I. Secondary vestibular neurons. *J Neurophysiol* 70:828–843
4. Scudder CA, Fuchs AF (1992) Physiological and behavioural identification of vestibular nucleus neurons mediating the horizontal vestibuloocular reflex in trained rhesus monkeys. *J Neurophysiol* 68:244–264
5. Roy JE, Cullen KE (1998) A neural correlate for vestibulo-ocular reflex suppression during voluntary eye-head gaze shifts. *Nat Neurosci* 1:404–410
6. McCrea RA, Gdowski GT (2003) Firing behaviour of squirrel monkey eye movement-related vestibular nucleus neurons during gaze saccades. *J Physiol* 546:207–224

7. Chen-Huang C, McCrea RA (1999) Effects of viewing distance on the responses of vestibular neurons to combined angular and linear vestibular stimulation. *J Neurophysiol* 81:2538–2557
8. Angelaki DE, Green AM, Dickman JD (2001) Differential sensorimotor processing of vestibulo-ocular signals during rotation and translation. *J Neurosci* 21(11):3968–3985
9. Meng H, Green AM, Dickman JD, Angelaki DE (2005) Pursuit – vestibular interactions in brain stem neurons during rotation and translation. *J Neurophysiol* 93(6):3418–3433
10. McConville KM, Tomlinson RD, Na EQ (1996) Behavior of eye-movement-related cells in the vestibular nuclei during combined rotational and translational stimuli. *J Neurophysiol* 76:3136–3148

Positive Feedback Control

Definition

A mechanism used to regulate the value or time course of an output variable or signal when the output variable is determined by the value of an input signal or the time course of an input signal. The control mechanism is said to be closed loop when the value of the output variable is sensed or measured, is fed back and compared to some desired reference value and is then used to determine the value of the input signal. The closed loop control mechanism is referred to as positive feedback control when a given change in the output variable produces a change in the input signal that causes a further change in the output in the same direction.

Positive feedback control is often unstable, but when appropriately configured systems can remain stable while using positive feedback control.

► Posture – Sensory Integration

Positive Schizophrenic Symptoms

Definition

Symptoms associated with reality distortion; most frequently auditory hallucinations (hearing voices), feeling of being observed or persecuted.

► Schizophrenia

Positron Emission Tomography

SVYATOSLAV V. MEDVEDEV

Institute of the Human Brain of the Russian Academy of Sciences, Laboratory of the Positron Emission Tomography, St-Petersburg, Russia

Definition

Positron emission tomography (PET) is a nuclear imaging technique that allows quantitative evaluation of biochemical and physiological processes in vivo, by using ▶**radiopharmaceuticals** (RPs) labeled with short-lived positron-emitting radionuclides, which are detected by their annihilation radiation with electronic coincidence detector systems.

Purpose

PET can be used in both research and clinical purposes for quantitative mapping of various physiological and biochemical processes. A number of these processes depend on the ▶**radiotracers** available.

Clinical Purpose

Oncology: The most common application of PET is to determine the presence, severity and staging of cancer, its recurrences and responses to treatment. In neuro-oncology, PET has been found useful for the differentiation between radiation necrosis and ▶**glioma** recurrence with 2-¹⁸F-2-deoxy-D-glucose (▶**FDG**) (less with labeled amino acids), glioma grade determination (FDG), and guidance for biopsy [1].

Whole-body FDG-PET enables the identification of primary lesions as well as local recurrence, lymph node involvement and distant metastases; so far, it has been quite a useful technique for tumor staging. PET provides more benefits for patients with non-small cell lung cancer (NSCLC), malignant melanoma, breast cancer, lymphoma, and colorectal cancer. PET also proved to be useful in radiation-treatment planning as well as in monitoring treatment responses (radio- or chemotherapy) [2,3].

Neurology: PET has significant implications in making a precise diagnosis of various ▶**neuropsychiatry** and ▶**movement disorders**. Clinical application includes lateralization of epileptic foci in ▶**temporal lobe epilepsy** prior to surgery (FDG or rarely ▶**FMZ** – flumazenil); differentiation between various types of ▶**dementia** (FDG); assessment of dopaminergic neuron degeneration in ▶**Parkinsonism** (6-FDOPA); and recognition of ▶**depression syndrome** (WAY100635) [4].

Cardiology: PET is a modern tool for quantitative measurements of myocardial blood flow (¹³N-ammonia; ⁸²Rb) and assessment of myocardial viability (FDG), and provides important criteria for a patient's selection

for a revascularization. Imaging of the ▶**sympathetic nervous system** with PET is possible but not very common in clinical cardiology [5].

Research

The most common research [4,6] application of PET involves ▶**activation studies** using high-sensitivity imaging of regional cerebral blood flow (rCBF) from multiple [¹⁵O]water injections. The alteration in neuronal activity in particular brain regions correlates with rCBF changes and the under performance of particular activities. Thus, PET is used to examine the spatial brain organization of the maintenance of cognitive, sensory, motor, emotional and other processes and responses to drug application.

Due to its high sensitivity and high specific activity (SA, the amount of radioactivity per mole) of the radiotracers, PET allows one to obtain quantitative information about the distribution of the target receptors throughout the brain, their affinity and density. The results are employed in fundamental studies of the pathogenesis of various neuropsychiatric disorders.

PET is a modern tool for the quantitative evaluation of drug-binding sites in living humans. By conducting PET studies with a suitable ▶**radioligand** before and after treatment by a drug, the fraction of the total number of binding sites that are occupied by the drug can be quantified (“drug occupancy study.”) Thus, the mechanism of drug action and optimal dosage can be evaluated in a very safe manner using the so-called “PET micro-dosing concept.” With this approach, the number of patients to be studied in phase II clinical trials can be minimized from thousands to tens, resulting in a reduction in the time and costs of the studies.

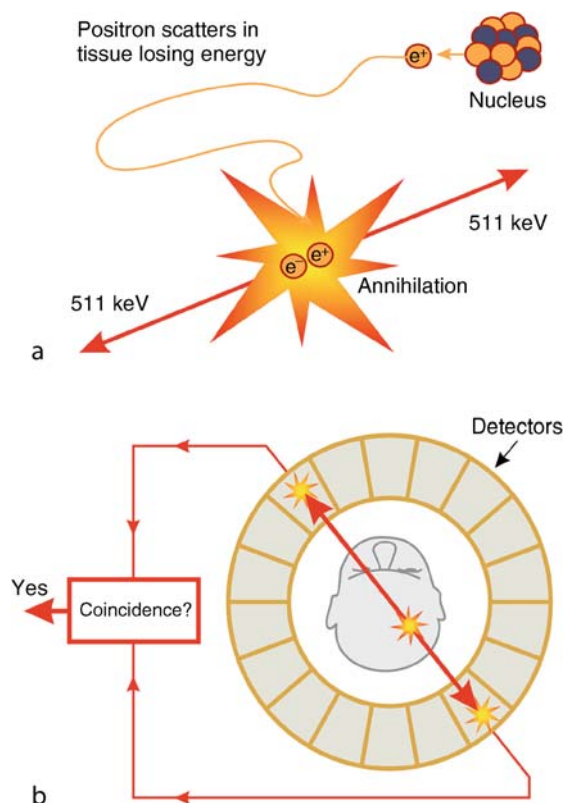
Principles

Basic Principles in PET Imaging

When a PET [4,7] ▶**radionuclide** is introduced into the human body, at any given time, part of the nucleus will decay emitting a positron (positively charged electron) and a neutrino. The neutrino leaves the body without interaction. The positron, after a series of scatterings, annihilates with an electron. As a result, two photons (gamma quantum) of equal energy, i.e., 511 keV, are emitted in opposite directions at almost 180° (Fig. 1a) and can be detected by an external detector system.

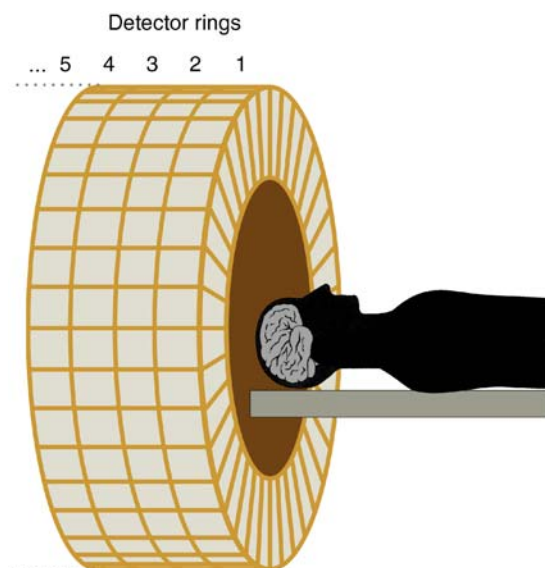
If arrays of gamma detectors are gathered around the body, a coincident event – simultaneous signal from a pair of detectors – means that annihilation took place somewhere on the straight line (line of response) connecting this pair (Fig. 1b).

The next annihilation induces coincident events, usually in another pair of detectors, and gives another line of response. The density of all intersections of such lines yields a spatial distribution corresponding to the



Positron Emission Tomography. Figure 1 (a) When a PET radionuclide is introduced into the human body, at any given time part of the nucleus will decay emitting a positron. After a series of scattering, the positron annihilates with an electron. As a result, two photons (gamma quantum) of equal energy, i.e., 511 keV are emitted in opposite directions very close to 180° apart. (b). If arrays of gamma detectors are gathered around the body, a coincidence event – simultaneous signal from a pair of detectors – means that annihilation took place somewhere on the straight line (line of response) connecting this pair.

isotope concentration map. This method of coincidence registrations is the essence of PET and provides for its high efficiency. Information is contained in the direction of the photon movements. In other systems such as gamma cameras, this information is provided by using special metal tubes – collimators, which allow only the minority of all photons to enter the collimator and thus reach the detectors, while the majority is absorbed in the metal. Thus, in this system, each detector detects only photons coming from one given direction. The coincidence mode of registration and the use of short-lived radionuclides (2–110 min half-life) mostly contribute to the high sensitivity of PET, which allows the detection of pikomole amounts of substances. As a result, studies of drug abuse (cocaine, amphetamine) and toxic compounds become possible



Positron Emission Tomography. Figure 2 A PET scanner consists of up to 30,000 detectors (scintillation crystals with photomultipliers), arranged in rings, formed in a cylinder around the body.

at concentration levels that do not cause any pharmacological effect [8].

A PET scanner consists of up to approximately 30,000 detectors (scintillation crystals with photomultipliers) arranged in rings formed in a cylinder around the body (Fig. 2).

These detectors involve a coincidence registration circuit, which collects information about coincidence events – counts. Using conventional algorithms for image reconstruction including different types of corrections, a volume isotope concentration map can be obtained. The unique feature of the PET coincidence technique is that corrections for radiation losses can be performed within the body (attenuation correction). This procedure is called “transmission scan.”

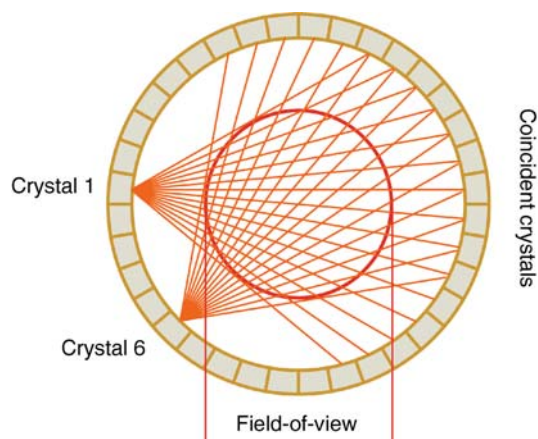
Theoretically, the spatial resolution of PET scanners is limited by physical characteristics of positron flight within the tissues. When a positron is emitted, it travels a short distance from the nucleus, typically about 2–8 mm maximum range. It loses its kinetic energy during this flight and then annihilates with an electron. It is the distance between the decaying nucleus and the point of annihilation, and the fact that the annihilation photons are not emitted at exactly 180° apart (deviation from 180° is up to 0.25°), which ultimately limit the spatial resolution of PET brain scanners to 4–5 mm (on average). However, in general, PET offers higher resolution than compared with 7–15 mm for single-photon emission computer tomography (SPECT).

PET allows registration of the counts per pixel, which are later transformed to counts per minute per ml of

tissue. However, in the counts acquisition process, the allowable radiation dose (regulated by the authorities) and limited acquisition time (depends on the instrumentation and study protocol) have to be considered. The result may be a poor [▶signal-to-noise ratio](#), which can be overcome by the use of spatial filtration. The latter is an additional source for degradation in resolution.

In general, the collection time varies from tens of seconds to tens of minutes. It is like an exposition time in photography and creates a strong limitation to the study protocol. Only steady states or at least quasi-steady or periodic processes should be investigated during one scan.

In modern PET scanners for data acquisition, so-called 2D and 3D modes are widely accepted. In the 2D mode, special septa between rings are installed to reduce the effect of scattering and random coincidence.

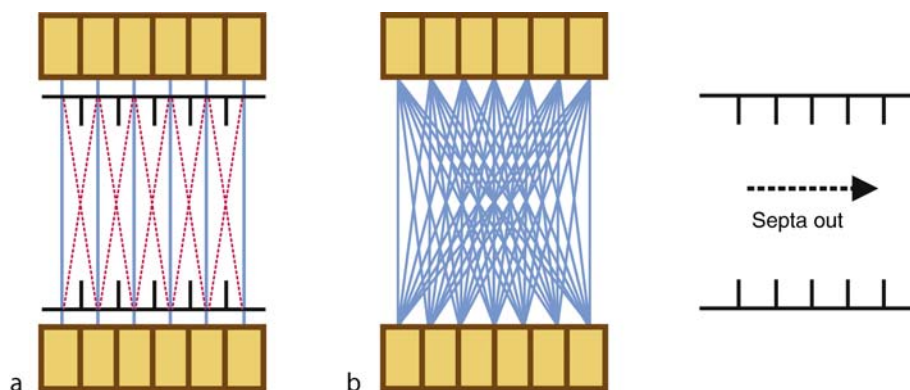


Positron Emission Tomography. Figure 3 Each detector of the ring forms a fan with a number of opposite detectors. Overlapping of all fans forms the field of view.

As a result, each detector forms three fans between itself and an array of other detectors of the ring (Fig. 3) as well as the two nearest rings.

As a result, there is a reconstruction of three slices: one in the ring and two so-called cross slices. It means that 15 rings give 29 slices. This procedure gives better resolution and accuracy, but is rather wasteful because many lines of response between other rings are not collected. If the septa are retracted, coincidences are admitted from large axial acceptance angles. The 3D mode allows increasing the number of counts by five times. This results in increases of necessary computing resources and, what is more important, in increases of mis-positioned events caused by scattered photons and in the registration of accidental coincidences, including some caused by photons outside the field of view. This, however, reduces resolution and quantitative accuracy. On the other hand, the 3D mode allows the reduction of the injected dose, and/or the duration of study, and/or improving the signal-to-noise ratio. The 3D mode is mainly used in neurophysiology, where the duration of scan is important. The 2D mode is more often applied in oncology (Fig. 4).

Finally, PET provides a map of spatial distribution of a positron-emitting isotope density in the field of view of the rings. When a compound labeled by this isotope is introduced into humans (usually by intravenous injection), it distributes within the body via the blood circulation in accordance with the delivery, uptake, metabolism and excretion of the particular tracer. To translate the measured radioactivity distribution into functional or physiological parameters, compartment models are used for the radiotracers with known metabolism. One of the most important characteristics of cell functioning is energy consumption. It can be compared to “gasoline consumption” in an engine, so for the living cells, the gasoline is glucose. However, it is like a gas that an engine absorbs and excretes.



Positron Emission Tomography. Figure 4 *Left:* 2D mode. Septa allow each detector to form lines of responses between itself and an array of detectors of the same ring and the two nearest rings only. *Right:* 3D mode. Lines of responses between all rings are allowed.

$2\text{-}^{18}\text{F}$ -2-deoxy-D-glucose (FDG), a glucose analog, has a similar rate of consumption as normal glucose, but a different way for excretion. It is accumulated in a cell at a rate proportional to the energy consumption (metabolism) of this cell. Therefore, PET with FDG allows direct assessment of the level of glucose consumption, which is one of the most important processes responsible for vital functions [6]. As glucose metabolism is greatly enhanced in malignancies, FDG is the most important and popular radiotracer for PET oncology. In fact, this tracer has many other applications in neurology and cardiology and is considered the “working horse” of PET (like ^{99}mTc in conventional nuclear medicine).

In addition to the high sensitivity (see above), the use of short-lived radioisotopes allows injection of a relatively high activity of the tracer (185 MBq for FDG brain scan), leaving the total radiation dose within acceptable limit. As PET radionuclides belong to the major elements of life, unlimited numbers of radiotracers can be prepared to track various physiological processes. In practice, although more than 2000 RPs have been evaluated in PET, no more than 10–15 specimens have been introduced into clinical routines. The reasons are the difficult synthesis and the necessity for automation in operating high levels of radioactivity, high running costs, and very strict regulations.

The logic of a PET study is as follows. First, a field of interest has to be specified (i.e., neurophysiology, oncology, and cardiology). Within this field (let's say oncology), the process of interest has to be identified (glycolysis or amino acid transport) and an appropriate tracer considered (FDG or ^{11}C -methionine). The next steps are radiotracer synthesis and PET study design using an appropriate pharmacokinetic model, after this the PET study itself. The final stage is data processing and assignment of the image to the pathology under study.

It should be emphasized that PET is a functional imaging technique, giving an isotope distribution map, which reflects a particular biochemical process, not the anatomy. The introduction of a hybrid system (PET-CT: PET-computer tomography) has greatly enhanced the performance and accuracy of PET imaging. The CT component is used to relate the signal of radiotracer to anatomical landmarks and to correct for non-uniform attenuation (instead of traditional transmission scans) [3].

PET Radionuclides

PET employs radiotracers (radiopharmaceuticals, RPs) labeled with short-lived positron-emitting radionuclides [9]. The four conventional radionuclides are: ^{15}O (half-life $T_{1/2} = 2$ min); ^{13}N ($T_{1/2} = 10$ min); ^{11}C ($T_{1/2} = 20.4$ min) and ^{18}F ($T_{1/2} = 110$ min). Carbon, oxygen, and nitrogen are elements of life and the building blocks of nearly every molecule of biological importance.

A fluorine-18 is often used to replace a hydrogen atom or hydroxyl group in a molecule.

Due to this short half-life, the PET radionuclides have to be produced in the vicinity, normally with a small dedicated cyclotron. PET cyclotrons accelerate charged particles (protons, deuterons) at a fixed energy (10–18 MeV for protons). Modern PET cyclotrons are negative-ions machines, which are characterized by an easy extraction process and dual beam option. PET radionuclides are produced in cyclotron targets via various nuclear reactions and delivered into a shielded hot cell by either gas flow (^{15}O , ^{11}C) or extra-pressure of helium (^{13}N , ^{18}F).

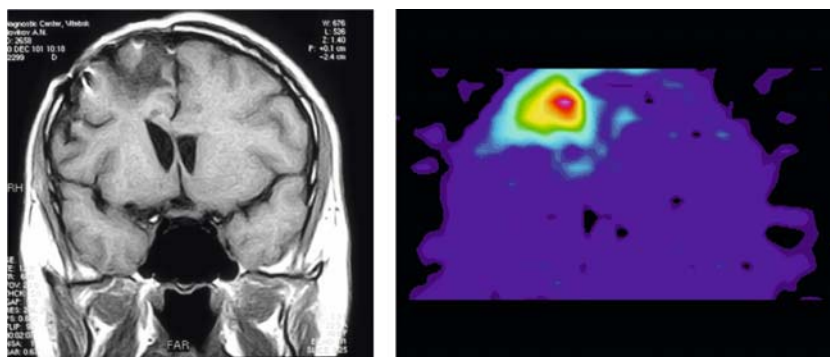
PET Radiopharmaceuticals

For PET applications, the radionuclides have to be tagged to specific pharmaceuticals, referred to as “radiopharmaceuticals” [10]. PET radionuclides are produced in a simple chemical form. They have to be transferred into tracers of interest via a complex synthesis using special automated modules.

The 2-min half-life of ^{15}O is very short; therefore, only very simple radiotracers like water- ^{15}O and ^{15}O -butanol are produced as rCBF agents. Quite rarely, ^{15}O -labelled gases are used in inhalation studies. ^{13}N -ammonia ($T_{1/2} = 10$ min) is available from a cyclotron target to fulfill the needs of heart-perfusion tracers.

The chemistry of carbon-11 ($T_{1/2} = 20$ min) is extensively developed. Depending on the target gas, ^{11}C is taken from the target in the form of $^{11}\text{CH}_4$ or $^{11}\text{CO}_2$. The latter is a versatile agent for labeling of carboxylic acids, such as $1\text{-}^{11}\text{C}$ -acetate, a tracer for oxidative myocardial metabolism. Most of the ^{11}C -preparations are based on ^{11}C -methylations, including $\text{L-}^{11}\text{C}$ -methyl-methionine, a second important tumor-seeking agent after FDG. Receptor radioligands such as ^{11}C -SCH23390 (D_1), ^{11}C -raclopride (D_2), ^{11}C -PE2I (dopamine transporter), ^{11}C -MADAM (serotonin transporter), ^{11}C -flumazenil (central BZ), ^{11}C -PK1195 (peripheral BZ), and ^{11}C -OH-BTA1 (β -amyloids) are obtained by this method.

The longest-living ^{18}F (110 min), allows several doses of the RPs to be obtained in one batch and to be delivered to other hospitals without access to a cyclotron. Irradiation of ^{18}O -enriched water by protons is most commonly used for generating high amounts of ^{18}F (35–70 GBq). Radionuclide is used in nucleophilic fluorination reactions to produce FDG. Although FDG is used in more than 80% of the routine PET studies, it is not a specific tracer for tumors as it enters other glucose-utilizing cells. New radiotracers for accurate characterization of tumors include $O\text{-(2'-}^{18}\text{F}\text{-fluoroethyl)-L-tyrosine}$ (FET) or $2\text{-[}^{18}\text{F}\text{]fluoro-L-tyrosine}$ (2-FTYR). Due to the low accumulation in gray matter, these amino acids provide higher contrast



Positron Emission Tomography. Figure 5 Patient after tumor removal and radiotherapy. *Left:* MRI diagnosis splits between radiation necrosis and recurrence of tumor. *Right:* PET with ^{11}C -methionine proved recurrence.

images of brain tumors. FLT, a labeled thymidine analog, was introduced for prognostic assessment and evaluation of responses to anti-proliferative therapy in colorectal, lung and other cancers. Assessment of tumor hypoxia using hypoxia markers (^{18}F -FMISO, ^{18}F -FAZA) allows one to select patients for treatments specifically designed to attack poorly oxygenated (hypoxic) tumor cells.

Data Processing and Analysis

Modern software for PET data processing and analysis usually includes means for: (i) preliminary data processing (smoothing, filtering, co-registration of images from different modalities, spatial normalization, i.e., image deformation to match the standard one); (ii) data 2D and 3D visualization; and (iii) statistical analysis. The most widely used software for research environment is the Statistical Parametric Mapping (SPM) software package (<http://www.fil.ion.ucl.ac.uk/spm/>).

For some study purposes (activation study, some studies in oncology), it is often enough just to compare the numbers of counts from different body areas without calculating the real concentration of the radiotracer.

Advantages and Disadvantages

At present, single-photon emission computer tomography (SPECT) makes up the majority of nuclear medicine procedures, mostly due to lower costs and availability of radiotracers from commercial sources (^{123}I , ^{111}In) or isotopic generators ($^{99\text{m}}\text{Tc}$). Due to the higher sensitivity of PET, the detectable amounts of molecules are lower than with SPECT. This is extremely important for receptor and drug development studies with very low amounts (pikomoles) of the substances involved. Unlike SPECT, PET allows a quantitative evaluation of the results using tracer kinetic modeling. In clinical studies, PET is usually used after ►magnetic resonance imaging (MRI) studies, and sometimes PET results can radically change a diagnosis

(Fig. 5). In whole-body PET studies, PET highlights peculiarities, which exist but are unrecognizable on MRI images. Due to the unlimited number of natural substrates, substrate analogs and drugs that can be labeled, PET allows the study of practically all varieties of physiological processes.

The major limitations of PET are the complexity of PET studies, high capital investments and running costs for the production of RPs requiring an on-site cyclotron. Recently, FDG has been delivered over distances corresponding to 2 h flight. Many stand-alone PET scanners are installed and served from one central “cyclotron/radiochemistry factory.” PET has proved to be cost-effective in staging and managing of certain malignancies such as NSCLC, by reducing the overall health care reimbursement. Due to the higher diagnostic accuracies of PET procedures, patients always benefit, even though the costs may be higher than with CT or MRI, which basically rely on morphological changes for tumor detection.

With respect to activation studies, functional MRI (fMRI), using the ►blood oxygenation level-dependent (BOLD) contrast method with echo-planar imaging, competes with PET. However, high levels of noise and ►claustrophobia effects result in several limitations in cognitive function assessments using this technique.

References

1. Wiebe LI (2004) PET radiopharmaceuticals for metabolic imaging in oncology. *Int Congr Ser* 1264:53–76
2. Bergstrom M, Grahnen A, Langstrom B (2003) Positron emission tomography microdosing: a new concept with application in tracer and early clinical drug development. *Eur J Clin Pharmacol* 59:357–366
3. McQuade P, Rowland DJ, Lewis JS, Welch MJ (2005) Positron-emitting isotopes produced on biomedical cyclotrons. *Curr Med Chem* 12(7): 807–818
4. Mazziotta JC, Toga AW, Frackowiak JRS (2000) Brain mapping. The Disorders. Academic Press, New York
5. Dobrucki LW, Sinusas AJ (2005) Cardiovascular molecular imaging. *Semin Nucl Med* 35:73–81

6. Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC (1997) Human brain function. Academic Press, New York
7. Zanzonico P (2004) Positron Emission Tomography: a review of basic principles, scanners design and performance, and current systems. *Semin Nucl Med* 34:87–111
8. Fowler JS, Ido T (2002) Initial and subsequent approach for the synthesis of 18FDG. *Semin Nucl Med* 32:6–12
9. McQuade P, Rowland DJ, Lewis JS, Welch MJ (2005) Positron-emitting isotopes produced on biomedical cyclotrons. *Curr Med Chem* 12(7):807–818
10. Welch MJ, Redvanly CS (2003) Handbook of radio-pharmaceuticals. Radiochemistry and application. Wiley, London, p 848

Posner Paradigm

Definition

► Visual Attention

Possibilism

Definition

The view that possible worlds exist in addition to the actual world and have the same ontological status.

► Possible World

Possible World

VOLKER GADENNE

Department of Philosophy and Theory of Science,
Johannes-Kepler-University Linz, Linz, Germany

Definition

A possible world is a complete way things might be. Possible worlds are alternative worlds one of which is the actual world. Philosophers use the notion of a possible world to define and discuss ideas such as possibility or necessity.

Description of the Theory

Leibniz's Idea of a Possible World

Consider the actual world, that is, the whole of what is the case, not only here and now but also in the past and in the future throughout all time. Thinking how

things are in the actual world, lots of other worlds can easily be imagined, simply by changing one or more features. In one possible world Schubert composed one more symphony. In another world, the dinosaurs did not die out, with all consequences and so on. Even the slightest difference, say one more atom in this table, makes a world different from the actual one.

Note that changes of states of affairs may have consequences. Some things that are possible in separate worlds are not possible in combination. There is a possible world in which George visits a conference in 2004 and there is another possible world in which George dies in a car accident in 2003. But there is (probably) no possible world that contains both these states of affairs.

Leibniz used the idea of possible worlds in his philosophy of creation. God had in his mind infinitely many worlds he could have created. He chose the best of these possible worlds and made it actual. On the basis of this theory, Leibniz attempted to provide a ► *theodicy*, a “justification of God” in the face of all the evils in the actual world. God had perfect reason to bring into existence the actual world despite all pain and suffering it contains, since it is the best of all possible worlds. Leibniz was convinced that even god could not create anything. He could have made other laws of nature, but not worlds that are logically impossible. [*Vielleicht genauer: Leibniz’ Gott kann logisch Unmögliches nicht schaffen, wohl aber nomologisch unmögliches].

Modal Logic and Possible World Semantics

The concept of possible worlds plays a central role in ► *modal logic*. Kripke [1,2] was most influential on the development of ► *possible world semantics* and its application to metaphysical problems (for an introduction, see [3]). Modal claims are fundamental to the ways the world is talked about. Consider, for example, the sentence: “There might be ten planets.” This is a sentence in the mode of *possibility*. Another modal notion is *necessity*, as in the sentence: “Bachelors are unmarried.” [*Sollte man hier den modalen Charakter nicht explizit machen so wie in dem vorangegangenen Beispiel?] What makes such statements true or false? According to the traditional view, modal statements are made true or false by relations of ideas or by linguistic conventions. In this example, the meaning of “unmarried” is part of the meaning of “bachelor.” However, some philosophers find it hard to see how all ► *propositions* thought to be necessarily true should be true by convention. How could the way that a thing is talked about make it true, e.g. that John is a human being or that infinitely many primes exist? Here the idea of possible worlds has its part. With its help the proposition may be expressed as follows. “There is at least one possible world in which the sun has exactly ten planets.” Necessity can be defined as truth in all

possible worlds. “In all possible worlds bachelors are unmarried.” “In all possible worlds there are infinitely many primes.”

Generally speaking, to say that a proposition is true is just to say that it is true in the actual world. But to say that a proposition is necessary or necessarily true is to say that it is true in every possible world. And to say that a proposition is possible or possibly true is to say that it is true in some possible world. According to this theory, the modal notions of necessity and possibility are explained in terms of quantification over worlds. In order to speak of a proposition p as necessarily true, a *universal quantifier* over worlds is needed. “For all possible worlds W , p is true in W .” To speak of a proposition p as possibly true, an *existential quantifier* over worlds has to be used. “There is at least one possible world W , such that p is true in W .”

Logicians found that on this neo-Leibnizian account they could give clear sense to the modal notions as they function in the various modal logics. Further concepts such as “validity,” “soundness” and “completeness” can be defined in terms of models constructed from sets of alternative worlds. Important results have been obtained by these methods (which can however not be presented here since they require a lot of technical details).

Modal notions are central to many of the traditional areas of philosophy, e.g. the nature of causation or free will. These notions have traditionally been challenged by empiricists. The most prominent critic was Quine [4]. In the 1950s, many philosophers became convinced that the ideas of necessity and possibility could have no place in philosophy. The development of possible world semantics gave many of them new reason to believe that the empiricist challenge can be met.

The Existence of Possible Worlds: Possibilism and Actualism

One of the most difficult problems of possible world theories concerns the ontological status of such worlds. The quantification over worlds seems to require that all these worlds exist. There are two main views dealing with this question, ►*possibilism* and ►*actualism*. For *possibilism*, as held by Lewis [5], there really is a plurality of possible universes of the same kind as this one. Each of them is conceived as a very comprehensive *concrete object*, having as its parts less comprehensive concrete objects such as stones, trees and persons. All the concrete objects that inhabit the various possible worlds are fully real. They are supposed to be really out there. Lewis denies that this world, which is called the “actual” one, has a special ontological status. The actual world is just a part of total reality, it is the part spatially and temporally related to this world. There is however no causal interaction between different possible worlds, because each of them is spatiotemporally closed.

Can the same individuals exist in different worlds? Lewis denies this. There are no “transworld individuals.” Each object exists in just one possible world. But how can he then account for the idea that there are different ways the same things could have gone? Instead of relating different possible worlds by strict numerical identity of some objects he ties them by what he calls the “counterpart relation.” For example, a particular person is in the actual world and no other, but has “counterparts” in several other worlds. The counterpart is not really the person, but it resembles the person closely in important respects.

Lewis argues for his theory by emphasizing its fruitfulness. Starting with the concept of a possible world as a primitive and with the means of set theory, he could not only define necessity and possibility, but also concepts such as “property” or “proposition.” His theory is committed to the program of an austere ►*nominalism*. Properties and propositions are reduced to sets of concrete objects. However, many philosophers find it hard to accept that all those possible objects should be regarded as fully real. The strict nominalistic account of modal notions was also criticized. It leads to some unsatisfactory consequences.

Another view about the existence of possible worlds is ►*actualism*. Actualists too, start with the assumption that the actual world is not the only possible world. But unlike possibilism, actualism gives the actual world a special ontological status. Only what actually exists, exists at all. This seems to imply that possible worlds do not exist. However, not all actualists draw this consequence. The leading advocates of actualism, like Plantinga [6] and Stalnaker [7], rather think that possible worlds can be identified with something that belongs to the actual world. To express this idea, they do not restrict themselves to the resources of nominalism, but refer to abstract entities (►*abstract entity*), especially, states of affairs. Every possible ►*state of affairs* is supposed to *exist in the actual world*. However, not all states of affairs *obtain*. Not everything that might be the case (and therefore exists as a state of affairs) is really the case (obtains). For example, the state of affairs that Aristotle became Plato’s successor at the academy exists, but failed to obtain.

Possible worlds are regarded by Plantinga as “maximally comprehensive possible states of affairs.” This is a possible state of affairs, W , so comprehensive that, for any state of affairs S , W either includes S or precludes S (and thus encompasses a whole world). As a consequence, all the possible worlds *exist*. But only one of them *obtains* – the *actual* world. Possible worlds are *abstract entities*, not concrete objects (►*concrete entity*). The same individuals can exist in different possible worlds. Actualism therefore needs no counterpart relation. Possible world theories raise a lot of problems, technical ones as well as metaphysical

difficulties, which are still unsolved. Nevertheless many philosophers are convinced of the fruitfulness of this program.

Applications to Other Fields

The notion of a possible world has been applied to several areas of philosophy to formulate and discuss special problems, e.g. in the philosophy of mind. Kripke [2] himself used it to analyze *mind-brain identity* and he argued against identity theory. Roughly, the structure of his argument is identity theory implies that pain is identical with a certain type of brain state. Such an identity statement would have to be necessarily true, i.e. true in all possible worlds, if it was true at all. But the tie between pain and a certain type of brain state is plainly contingent. Therefore, they cannot be identical.

A central idea of contemporary philosophy of mind is *supervenience*. Kim [8] analyses mind-brain supervenience in terms of possible worlds. The assumption that two persons with the same brain states must necessarily have the same mental states can be formulated as follows. "Mental properties supervene on physical properties in that if any *x* (in any possible world) and *y* (in any possible world) have the same physical properties (in their respective worlds), then *x* and *y* have the same mental properties (in those worlds)."

References

1. Kripke SA (1963) Semantical considerations on modal logic. *Acta Philos Fenn* 16:83–94
2. Kripke SA (1980) Naming and necessity. Harvard University Press, Cambridge
3. Loux MJ (1998) *Metaphysics*, Chap 5. Routledge, London
4. Quine WVO (1960) Word and object. MIT, Cambridge
5. Lewis DK (1986) On the plurality of worlds. Blackwell, Oxford
6. Plantinga A (1974) The nature of necessity. Oxford University Press, Oxford
7. Stalnaker R (1984) *Inquiry*. MIT, Cambridge
8. Kim J (1996) *Philosophy of mind*. Westview, Boulder

Possible World Semantics

Definition

A type of formal semantics that uses the notion of a possible world as a central concept; formal semantics is the study of the interpretations of formal languages.

- Possible World
- Property

Postactivation Potentiation (PAP)

- Force Potentiation in Skeletal Muscle

Postcentral Gyrus

Synonyms

- Gyrus postcentralis

Definition

= primary somatosensory cortex = SI
= area 3 + 1 + 2

The postcentral gyrus lies in the parietal lobe directly behind the central sulcus. Observing strict somatotopic arrangement, the somatosensory tracts of the contralateral body half terminate here.

Conscious localization and differentiation of quality and intensity of a tactile stimulus are effected in cooperation with the postcentral gyrus. Lesions of the postcentral gyrus reduces the response to tactile, thermal and noci stimuli from the contralateral body half.

- Telencephalon

Posterior Cerebellar Lobe

Synonyms

- Lobus cerebelli post.; ► Posterior lobe of cerebellum

Definition

The posterior lobe is the part of the cerebellum caudal to the primary fissure, and is composed of vermis portions (declive, folium, tuber, pyramid and uvula) as well as hemisphere portions (simple lobule, semilunar, gracile and biventer lobules as well as tonsil). Functionally this subdivision has practically no significance, since the cerebellum evidences a functional arrangement in a vertical direction (vermis, intermediate part, lateral part).

- Cerebellum

Posterior Colliculus

► Inferior Colliculus

into more general ► **dementia**. Initially, elementary visual functions are lost, but then more complex syndromes show up, including visual agnosia, topographical problems, ► **optic ataxia**, simultanagnosia, ocular apraxia (► **Balint's syndrome**), right-left confusion, ► **alexia**, ► **acalculia**, ► **agraphia** (► **Gerstmann's syndrome**).

► **Balint's Syndrome**
 ► **Gerstmann's Syndrome**
 ► **Optic Ataxia**

Posterior Column

Synonyms

► Funiculus post; ► Posterior funiculus

Definition

The cuneate fasciculus and gracile fasciculus together form the posterior column and are the main axes of epicritic sensibility: – gracile fasciculus: it collects the epicritic fibers from the sacral, lumbar as well as lower thoracic cord and terminates in the gracile nucleus. – cuneate fasciculus: contains the fibers from the upper thoracic cord as well as from the cervical cord and terminates in the cuneate nucleus.

► Pathways

Posterior Horn

Synonyms

► Cornu post

Definition

He majority of primary afferents entering through the posterior horn terminate in the posterior horn of the spinal cord. Three zones can be distinguished:

- Marginal cells
- Substantia gelatinosa
- Nucleus proprius

► Medulla spinalis

Posterior Commissure

Synonyms

► Commissura post

Definition

Here cross the fibers that are vital for controlling vertical eye movement and consensual light reaction of the pupils, including fibers from the superior colliculus, pretectal region as well as tegmentum of Mesencephalon.

► Telencephalon

Posterior Lobe of the Hypophysis

Synonyms

► Neurohypophysis

Definition

The posterior lobe of the hypophysis is also called the neurohypophysis since it is composed of hypothalamic nervous tissue. Its proximal segment is formed by the tuber cinereum and infundibulum, and its distal segment is the posterior lobe of the hypophysis. Via the infundibular nucleus, axons of the paraventricular nucleus and of the supraoptic nucleus pass to the blood vessels in the posterior lobe, where they release the hormones ADH and oxytocin.

► Diencephalon

Posterior Cortical Atrophy

Definition

Degenerative disorder of the posterior part of the brain beginning with visual symptoms and then proceeding

Posterior Nuclei

Definition

The thalamic nuclei that project to the parietal somatosensory cortex, relaying nociceptive inputs from the periphery.

► Somatosensory Cortex I

Posterior Parietal Cortex (PPC)

Definition

Cerebral cortex posterior to the postcentral gyrus.

► Visual Space Representation for Reaching

Posterior Spinocerebellar Tract

Synonyms

► Tractus spinocerebellaris post

Definition

The posterior spinocerebellar tract carries primary afferents from the spinal cord to the cerebellum.

It has its origin in Clarke's column in the thoracic cord and conducts proprio- and exteroceptive impulses (skin receptors, muscle spindles, tendon spindles) from the posterior limbs to the cerebellum.

► Cerebellum

Posterior Tuberculum

Definition

A caudal part of the diencephalon present in cartilaginous and bony fishes that contains some dopaminergic neurons as well as several laterally migrated nuclei of the preglomerular nuclear complex that are involved in

the relay of ascending sensory pathways, particularly for the gustatory and lateral line systems.

► Evolution of the Somatosensory System: In Non-mammalian Vertebrates

Posterolateral Column

Synonyms

► Tractus postervlat. (Lissauer); ► Posterolateral tract (Lissauer)

Definition

The white matter between the ventral root and dorsal root gives rise to the lateral column, containing:

1. anterolateral column with
 - anterolateral fasciculus
 - parts of the anterior spinocerebellar tract.
2. posterolateral column with
 - posterior spinocerebellar tract
 - parts of the anterior spinocerebellar tract
 - lateral pyramidal tract.

► Medulla Spinalis

Posteromedial Barrel Subfield

► Barrel Cortex

Postganglionic Fiber (Neuron)

Definition

Ganglion neurons of autonomic ganglia all issue an axon (which turns into a nerve fiber), and virtually all these fibers exit the ganglion directed toward a peripheral target organ, along different paths depending on the ganglion of origin. Some form discrete nerves (splanchnic, pelvic, urinary), others reach somatic nerves and the mixed nerves of autonomic and somatic fibers thus formed reach the periphery (the limbs in particular and all the skin). The post-ganglionic fibers

can be very long and are usually unmyelinated, hence of slow conduction velocity. Upon reaching the target organ they branch extensively and make contact with muscle elements (mainly smooth muscle cells) and with secretory elements (glands). Post-ganglionic fibers exert their effect on muscle and glands by releasing neurotransmitters that stimulate (and sometimes inhibit) contraction and secretion. The neurotransmitters are released from “terminals” that are not only the expansions at the anatomical end of each nerve branch but also at bulbous expansion (varicosities) scattered along a substantial part of the terminal portion of the axons. Each ganglion neuron issues one fiber traveling to the periphery, which has many branches within the terminal organ, which have many thousands of varicosities along their terminal branches.

In the bladder muscle, for example, a few thousand ganglion neurons directly innervate millions of muscle cells. The exact relationship between varicosities (nerve endings) and muscle cells (or gland cells) varies from a close contact (a neuro-muscular junction) in some tissues (the bladder, for example) to a loose relationship with a wide gap (some blood vessels, for example).

- Autonomic Ganglia
- Parasympathetic Pathways
- Sympathetic Pathways

Postganglionic Nerves

Definition

Autonomic nerves going to the end organ, e.g., cavernous nerve and the dorsal nerve of the penis and clitoris.

- Sexual reflexes

Postganglionic Neurotransmitter

JUDY L. MORRIS, IAN L. GIBBINS
Department of Anatomy & Histology, and Centre for Neuroscience, Flinders University, Adelaide, SA, Australia

Synonyms

Autonomic neurotransmitter

Definition

Postganglionic autonomic neurons have their cell body in an ►autonomic ganglion and an axon that extends out to a target organ. These neurons regulate activity of most organs of the body by releasing combinations of neurotransmitters. Postganglionic neurotransmitters are released from multiple swellings along the axons, or ►varicosities, separated from the target cell membrane by gaps of 20–100 nm to form ►neuroeffector junctions (Fig. 1).

Each axon has thousands of varicosities that can release neurotransmitter from the postganglionic neuron. It is now clear that the earliest identified neurotransmitters, acetylcholine and noradrenaline (adrenaline in some non-mammalian vertebrates), do not mediate all actions of postganglionic autonomic neurons. Nearly all neurons releasing acetylcholine or noradrenaline also synthesize and release various combinations of other neurotransmitter molecules including adenosine triphosphate (ATP), nitric oxide (NO) and one or more neuropeptides such as vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) or opioid peptides [1,2,3,4,5]. Furthermore, many neurons intrinsic to the gastrointestinal tract or airways use nitric oxide, ATP and one or more neuropeptides but do not synthesize acetylcholine or noradrenaline (Table 1).

The release of more than one transmitter from the same postganglionic neuron, termed ►co-transmission, is now accepted as the rule rather than the exception. As well as regulating activity of the target organs (►postjunctional actions), transmitters released from postganglionic neurons can act back on terminals of the same or other nearby nerve terminals to alter further transmitter release (►prejunctional actions). Some transmitters have both pre-junctional and postjunctional actions, while others act at only one site (Fig. 1).

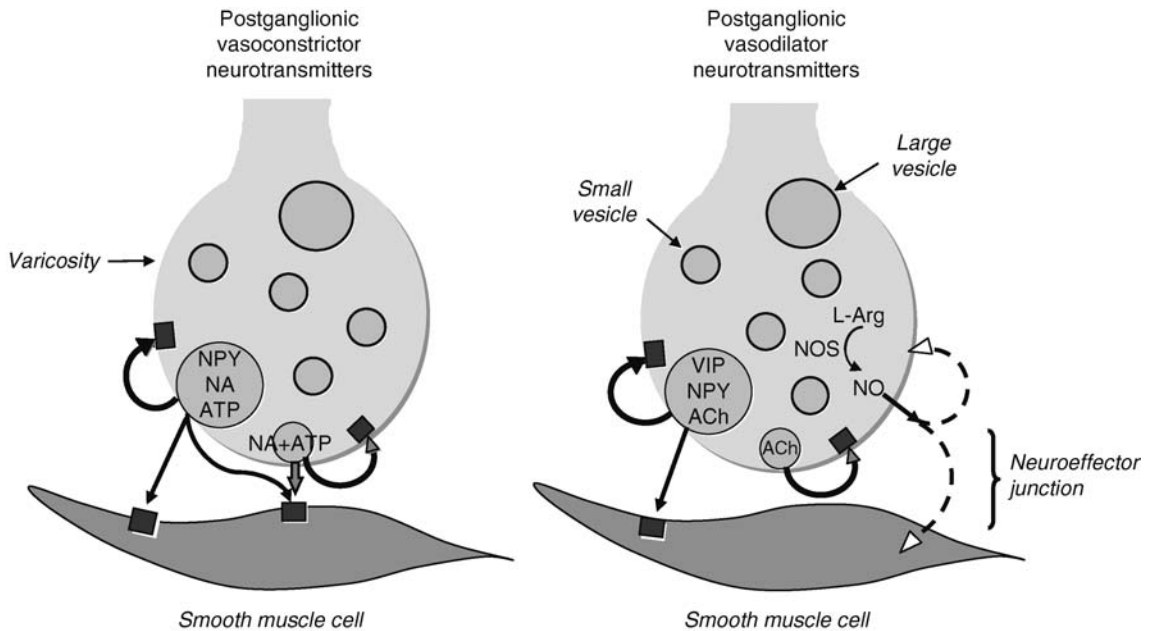
Characteristics

Quantitative Description

Twenty or more different molecules have been identified as neurotransmitters in postganglionic autonomic neurons including enteric neurons (Table 1). Some individual neurons contain five or more co-transmitters [1].

Higher Level Structures

Neurotransmitters are stored in membrane-bound vesicles within axon terminals. Synaptic vesicles can vary in size from small (40–60 nm diameter) to large (80–120 nm diameter). Nerve terminals contain both small and large vesicles in varying ratios. In varicose terminals of most postganglionic autonomic neurons, small vesicles are more abundant than large vesicles. Sometimes small vesicles tend to be clustered towards the cell membrane adjacent to the neuroeffector junction, but this is not always apparent. In contrast, large vesicles are not concentrated near the neuroeffector junction. Small vesicles



Postganglionic Neurotransmitter. Figure 1 Example of two types of postganglionic neurons releasing multiple neurotransmitters in a single blood vessel. Co-transmitters stored in and released from varicosities of postganglionic vasoconstrictor neurons and postganglionic vasodilator neurons into neuroeffector junctions with smooth muscle cells in the uterine artery (see [1]). Large vesicles in vasoconstrictor neurons contain noradrenaline (NA), adenosine triphosphate (ATP) and neuropeptide Y (NPY), while small vesicles contain only NA and ATP. Transmitters released from small and large vesicles can act on the postjunctional receptors on the smooth muscle cells to produce vasoconstriction, as well as prejunctional receptors on the membrane of the varicosity where they usually inhibit transmitter release. Nearby varicosities of vasodilator neurons contain large vesicles with acetylcholine (ACh), vasoactive intestinal peptide (VIP), NPY and several other peptides [6]. Small vesicles contain ACh alone. Nitric oxide is synthesized in the cytoplasm by nitric oxide synthase conversion of L-arginine, before diffusing across the neuroeffector junction and into smooth muscle cells to activate cyclic GMP and relax the smooth muscle. VIP has a potent vasorelaxant action, while ACh only has a prejunctional effect to inhibit neurotransmitter release. The function of NPY released from the vasodilator neurons is not known, but it may produce relaxation of an already constricted vessel and is likely to have a prejunctional inhibitory effect on transmitter release. It is likely that postganglionic neurotransmitters also can affect neurotransmission from adjacent varicosities.

in postganglionic neurons contain noradrenaline, ATP or acetylcholine. Large vesicles often contain neuropeptides in addition to non-peptide transmitters. Nitric oxide is an unusual neurotransmitter – it is not stored in synaptic vesicles but synthesized on demand in the nerve terminals (Fig. 1).

Lower Level Structures

The chemical structure of postganglionic neurotransmitters encompasses low molecular weight gases such as nitric oxide (and possibly carbon monoxide; [2]), purine nucleotides like ATP, catecholamines and acetylcholine, and neuropeptides ranging in size from less than a dozen amino acids (e.g., enkephalin, substance P) to more than thirty amino acids (VIP, NPY, calcitonin gene-related peptide (CGRP; Table 1). Almost all of these substances also are neurotransmitters in the central nervous system. The nature and sequence of neurotransmitters has been remarkably conserved through evolution, so that only very small if any chemical differences occur

between postganglionic neurotransmitters in different vertebrate classes.

Higher Level Processes

As in all other neurons using chemical neurotransmission, synaptic vesicles in postganglionic neurons release their neurotransmitters by exocytosis, and vesicle membranes are recycled at the nerve terminal. Large vesicles are formed in the cell body where they are packaged with a variety of proteins (such as neurotransmitter synthesizing enzymes and transporters) and neuropeptides, then are transported down to the nerve terminal. In some neurons post-translational processing of peptides such as dynorphin can occur within large vesicles as they are transported down the axon. The non-peptide transmitters noradrenaline and acetylcholine are synthesized or taken up into vesicles in the cell body, axon and terminals. In contrast, neuropeptides cannot be taken up and repackaged into vesicles at the nerve terminal. This differential processing of peptide and non-peptide transmitters may

Postganglionic Neurotransmitter. Table 1 Substances localized in postganglionic autonomic neurons of most vertebrates

Neurotransmitter	Molecular weight	Postganglionic neurons with neurotransmitter	Common co-transmitters
Acetylcholine (ACh)	146	Parasympathetic neurons.	NO, VIP, Som
		Enteric motor neurons, Enteric secretomotor neurons.	SP, NKA
		Subpopulation of sympathetic nerves e.g., sudomotor neurons	NPY, Som, Gal, CCK, CGRP
			VIP
Adenosine triphosphate (ATP)	507	Sympathetic neurons.	NA, NPY
		Pelvic nerves to the bladder.	Ach
		Enteric inhibitory neurons.	NO, VIP
Adrenaline (Ad, epinephrine)	183	Sympathetic neurons in amphibians, fish.	NPY
Noradrenaline (NA, norepinephrine)	169	Most sympathetic neurons in mammals, birds, reptiles.	ATP, NPY
Calcitonin gene-related peptide (CGRP)	3,807	Parasympathetic neurons.	ACh, NO, VIP
		Enteric secretomotor neurons.	ACh, NPY, Som, Gal, CCK, CGRP
Cholecystokinin (CCK8)	1,142	Enteric secretomotor neurons	ACh, NPY, Som, Gal, CGRP
Dynorphin (DynA1–17)	2,148	Sympathetic neurons.	NA, +/- NPY
		Enteric neurons.	VIP, NO, GRP
Enkephalin (Enk)		Some sympathetic neurons.	NA, +/- NPY
Met-Enk, Leu-Enk	574, 556	Enteric neurons.	Dyn, VIP, NO
Galanin (Gal)	3,211	Sympathetic neurons.	NA, +/- NPY
		Intrinsic cardiac neurons.	ACh, Som
		Enteric neurons.	
Gastrin releasing peptide (GRP)	2,806	Enteric neurons.	VIP, Dyn, Gal, NO
5-Hydroxytryptamine (5-HT, serotonin)	1,76	Taken up into and released from some sympathetic and enteric neurons	NA, NPY
			Ach
Neurokinin A (NKA)	1,133	Enteric motor neurons.	SP, Ach
Neuropeptide Y (NPY)	4,254	Many sympathetic neurons.	NA, ATP
		Some parasympathetic neurons.	ACh, +/- VIP
		Enteric secretomotor neurons.	ACh, Som, CGRP, CCK
Nitric oxide (NO)	30	Parasympathetic neurons.	ACh, VIP
		Enteric inhibitory neurons.	VIP, ATP
Peptide histidine isoleucine (PHI)	2,996	Most parasympathetic neurons.	ACh, VIP, PACAP
		Enteric inhibitory neurons.	VIP, NO, ATP
Pituitary adenylate cyclase activating peptide (PACAP) 38	4,538	Enteric neurons	VIP, GRP
		Parasympathetic neurons.	ACh, VIP, PHI
Somatostatin (Som)	1,638	Intrinsic cardiac neurons.	ACh, +/- Gal
		Enteric neurons.	ACh, NPY, CGRP, CCK
Substance P (SP)	1,348	Cranial parasympathetic neurons.	Ach
		Enteric motor neurons.	ACh, NKA
Vasoactive intestinal peptide (VIP)	3,326	Most parasympathetic neurons.	ACh, PHI, PACAP
		Enteric inhibitory neurons.	PHI, PACAP, NO, ATP

Details of co-transmitters derived mostly from animal studies, concentrational on guinea-pegs (see [1,4]). A definitive neurotransmitter role has been established for all substances in all locations listed. Many enteric neurons do not receive direct inputs from the central nervous system but form part of intrinsic neural circuits.

contribute to selective depletion of co-transmitters after intense activation of autonomic neurons. Nitric oxide is synthesized in postganglionic nerve terminals by the calcium-dependent enzyme, nitric oxide synthase (NOS), located in the cytoplasm and not in vesicles (Fig. 1).

The action potential-dependent exocytosis of neurotransmitters from small vesicles in all neurons, including postganglionic autonomic neurons, occurs through specific interactions between proteins located on the vesicle membrane and proteins attached to the inner surface of the nerve terminal membrane, the ►**SNARE proteins** (soluble NSF attachment protein receptor proteins). Exocytosis is a multi-step process that is calcium-dependent. First, the vesicles are released from a framework of actin filaments and move close to the terminal membrane where they become docked. This is followed by fusion of the vesicle membrane with the nerve terminal membrane, allowing release of vesicle contents into the extracellular space of the neuroeffector junction. Exocytosis of transmitters from small vesicles can be inhibited by botulinum neurotoxins that act intracellularly to cleave the SNARE proteins. However, it is not clear whether exocytosis of neuropeptides from large vesicles uses the same SNARE proteins that mediate small vesicle exocytosis. Release of neuropeptides from postganglionic autonomic neurons certainly is less sensitive to blockade by botulinum toxin than release of non-peptides from small vesicles [6]. Nitric oxide release from postganglionic autonomic neurons is completely resistant to botulinum toxin, confirming that this transmitter is not associated with vesicular storage and exocytosis.

Lower Level Processes

After release from the terminals of postganglionic neurons, noradrenaline, ATP and acetylcholine are rapidly removed from the neuroeffector junction by degradation or uptake by the nerve terminal and target tissue. These mechanisms limit the time course and distance over which the transmitters can act on prejunctional or postjunctional receptors. Nitric oxide acts on target tissues after diffusion across the membrane of both the nerve terminal and the postjunctional cell. This molecule diffuses rapidly from the neuroeffector junction and potentially can act outside the neuroeffector junction. However, superoxide radicals can rapidly inactivate nitric oxide, so diffusion of the transmitter away from the nerve terminal may be quite limited. Neuropeptides released from postganglionic neurons are not rapidly taken up across the pre- or postjunctional membrane and largely remain in the extracellular space until they are enzymatically degraded. This can result in neurally released neuropeptides interacting with receptors at considerable distances from the neuroeffector junction, a phenomenon called volume transmission. Nevertheless, neuropeptides bound to postjunctional receptors can be taken up into the

target cell via ►**endocytosis**, thus contributing to ►**receptor desensitisation**.

Process Regulation

The actions of postganglionic neurotransmitters can be regulated by altering synthesis, transport, release, breakdown or reuptake of the transmitter itself, by altering expression or availability of neurotransmitter receptors, or by altering intracellular messengers and ion channels mediating neurotransmitter actions in the target cell. The major regulator of postganglionic neurotransmitter release is the frequency and pattern of action potentials travelling down the postganglionic axon. This is determined primarily by the pattern of impulses leaving the central nervous system via preganglionic neurons. However, this pattern can be modulated by local and circulating hormones changing the excitability of postganglionic neurons in autonomic ganglia. The excitability of postganglionic neurons also can be changed by ongoing activation of sensory nerves passing through autonomic ganglia, such as happens in inflammation. The sensory neurotransmitter substance P, and the hormone angiotensin both increase the excitability of many postganglionic neurons so that they fire more often in response to the same pattern of preganglionic nerve activity. Many substances also can modulate the expression of neurotransmitters or their synthetic enzymes by altering gene transcription in the postganglionic nerve cell body, or affect the release of transmitter from the varicosities of postganglionic neurons.

Ultimately, the pattern of firing of postganglionic neurons determines which co-transmitters are released from the varicosities. With a low frequency of impulses, <2 pulses per second (Hz), the small vesicles preferentially release their transmitters, so catecholamines, ATP and acetylcholine are released without neuropeptides. NOS also can be activated by low impulse frequency, releasing nitric oxide. Generally, large vesicles containing neuropeptides are not released until impulse frequencies reach at least 5, and up to 20, per second. An irregular pattern of high frequency activation is more effective in releasing neuropeptides from large vesicles than is a continuous high frequency firing. This frequency-dependent release of co-transmitters allows postganglionic neurons to produce a wide range of actions on their target tissues.

Function

Neurotransmitters released from postganglionic autonomic neurons have a wide range of functions. They activate or inhibit target cells such as smooth muscle cells of blood vessels, viscera, airways and skin, cardiac muscle, secretory cells in many glands, and other neurons in autonomic ganglia including enteric neurons. These actions regulate vital processes such as

heart rate and arterial blood pressure, control of regional blood flow, the gastrointestinal system, respiration, reproduction and thermoregulation.

Many neurotransmitters can act both on the target tissue (postjunctional action), and back on the nerve terminal that released them (prejunctional action) to regulate further release of neurotransmitter (Fig. 1). Postganglionic neurotransmitters typically act via receptors on the target cell membrane that in turn can switch on or off a large array of second messenger pathways that influence intracellular calcium levels and usually affect membrane potential. Some transmitters, for example ATP, also can act via receptors that are themselves ion channels, called ionotropic receptors. In contrast, nitric oxide does not use receptors on the target cell membrane but diffuses freely across the membrane of both the nerve terminal and target cell, where it stimulates production of cyclic GMP. The detailed actions of multiple co-transmitters released from the same nerve terminal are not fully known. However, it is clear that some co-transmitters may have only a postjunctional action and some only a prejunctional action [1,6]. Further research also is required to clarify the roles of co-transmitters that potentially can have opposite effects on the target cells (Fig. 1). Nevertheless, the very different molecular sizes of co-transmitters, their different post-junctional signalling systems together with their different methods of inactivation, results in wide variations in the time course of neurotransmitter action. While noradrenaline, ATP, acetylcholine and nitric oxide typically have post-junctional actions lasting seconds to minutes, neuropeptide effects are slow in onset and can last up to tens of minutes, if not hours. Thus, release of neuropeptide transmitters by higher levels of impulse activity provides an efficient way to produce long-lasting functional changes in the target tissues.

Pathology

Pathological conditions involving dysfunction of the autonomic nervous system include those affecting post-ganglionic transmitter synthesis, release or post-junctional actions. Congenital deficiency in ►**dopamine- β -hydroxylase (DBH)** has been demonstrated in a small number of patients with autonomic dysfunction restricted to sympathetic pathways. These patients fail to synthesize adequate noradrenaline, and noradrenaline and adrenaline are undetectable in the plasma while plasma dopamine is elevated. The most obvious symptom is severe postural hypotension from an early age [7]. Other symptoms include ptosis and retrograde ejaculation. In contrast, some forms of hypertension involve hyperactivity of cardiovascular sympathetic nerves that results in increased release of noradrenaline from postganglionic neurons. This increased sympathetic activity is thought to be involved in both the development and maintenance of arterial hypertension [7]. Autoimmune neuropathies

affecting autonomic nerve function also can occur. Autoantibodies leading to autonomic dysfunction most often are directed at nicotinic receptors in autonomic ganglia. However, autoantibodies directed at muscarinic receptors on peripheral target tissues have been reported in Sjögren's syndrome and scleroderma. These antibodies prevent acetylcholine released from parasympathetic nerve terminals from producing secretion in the lacrimal and salivary glands via post-junctional muscarinic receptors, resulting in the characteristic sicca symptoms of the disease [8].

Therapy

Therapeutic interventions for autonomic dysfunction include use of a wide variety of agents affecting post-ganglionic transmitters. DOPS (dihydroxyphenylserine) is useful in overcoming DBH deficiency, as it is converted directly to noradrenaline by dopa-decarboxylase, thus alleviating the requirement for DBH ([7]. Antagonists for post-junctional β -adrenoceptors (beta blockers) are used widely to treat hypertension by reducing sympathetic cardio-excitation. In Sjögren's syndrome, agonists of M3 muscarinic receptors improve sicca symptoms, and use of antiidiotypic antibodies to neutralize autoantibodies has been proposed [8]. In conditions involving hyperactivity of postganglionic ►**cholinergic** nerves, such as hyperhidrosis, anticholinergic agents are sometimes used although surgical sympathectomy has long been the treatment of choice. Recently, botulinum neurotoxin treatment has been used to block exocytosis of acetylcholine from the sudomotor neurons. Botulinum toxin A (Botox) has been popular, but it has been suggested that botulinum toxin B (Neurobloc) might produce more prolonged therapy due to its decreased immunogenic nature [9]. Botox also is used increasingly to treat autonomic dysfunctions such as neurogenic urinary incontinence or oesophageal achalasia. Sildenafil (Viagra), an inhibitor of phosphodiesterase-5, is used for treatment of erectile dysfunction in males, although its benefit in females is more controversial. This agent enhances the action of nitric oxide released from pelvic autonomic nerves, by reducing breakdown of cyclic GMP in smooth muscle [10]. Thus, sildenafil is only beneficial if the pelvic nerve pathways are intact.

References

1. Gibbins IL, Morris JL (2000) Pathway specific expression of neuropeptides and autonomic control of the vasculature. *Regul Pept* 93:93–107
2. Baranano DE, Snyder SH (2001) Neural roles for heme oxygenase: contrast to nitric oxide. *Proc Natl Acad Sci* 98:10996–11002
3. Burnstock G (2004) Cotransmission. *Curr Opin Pharmacol* 4:47–52
4. Furness JB, Costa M (1987) The enteric nervous system. Churchill Livingstone, Edinburgh, p 290

5. Lundberg JM, Hökfelt T (1986) Multiple coexistence of peptides and classical transmitters in peripheral autonomic and sensory neurons – functional and pharmacological implications. *Prog Brain Res* 68:241–262
6. Morris JL, Jobling P, Gibbins IL (2001) Differential inhibition by botulinum neurotoxin A of cotransmitters released from autonomic vasodilator neurons. *Am J Physiol Heart Circ Physiol* 281:H2124–H2132
7. Bannister R, Mathias CJ (eds) (1993) *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system*, 3rd edn. Oxford University Press, Oxford, p 953
8. Cavill D, Waterman SA, Gordon TP (2003) Antiidiotypic antibodies neutralize autoantibodies that inhibit cholinergic neurotransmission. *Arthritis Rheum* 12:3597–3602
9. Nelson L, Bachoo P, Holmes J (2005) Botulinum toxin type B: a new therapy for axillary hyperhidrosis. *Br J Plast Surg* 58:228–232
10. Gibson A (2001) Phosphodiesterase 5 inhibitors and nitrgic transmission – from zaprinast to sildenafil. *Eur J Pharmacol* 41:1–10

Postherpetic Neuralgia (PHN)

Definition

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome and is the most common complication of herpes zoster (HZ, shingles). PHN occurs mainly in the 60 years plus age group and in individuals suffering more severe acute pain and rash with HZ. Herpes zoster (shingles, HZ) results from reactivation of varicella zoster virus (VZV), one of a family of human herpes viruses, which has remained latent in sensory ganglia following primary infection with varicella (chicken pox). The incidence of HZ increases with age reflecting an age related decline in cell mediated immunity (CMI).

►Neuropathic Pain

Post-inhibitory Rebound

Definition

The ability of a neuron to respond to a hyperpolarization with a depolarization of the membrane potential above the level of the normal resting membrane potential. This can either be due to the activation of a hyperpolarization- activated inward current, I_h , or the action of low-voltage activated inward current, $I_{Ca(T)}$, that is inactivated at the normal resting membrane potential. In

this case, hyperpolarization of the membrane potential removes the inactivation of the current, so that it can be activated when the membrane potential returns to its resting level at the end of the hyperpolarization. This activation causes a transient depolarization of the membrane potential, the post-inhibitory rebound, that can trigger action potentials.

- Calcium Channels – an Overview
- Central Pattern Generator
- Omnipause Neurons
- Stomatogastric Ganglion

Post-junctional

Definition

Post-junctional refers to the target cell distal to a neuroeffector junction, responding to neurotransmitters.

Post-saccadic Drift

Definition

In an ideal saccade, the eye rapidly accelerates and then abruptly stops so that gaze remains stationary during the subsequent period of fixation. In reality, many saccades are followed by continued eye movements that have sub-saccadic velocities (e.g., 2–30°/sec in primates) but sufficient durations to appreciably change the direction of gaze. These post-saccadic drifts may be onwards or backwards relative to the saccade, and have several origins. After undershooting saccades in cats, the superior colliculus may continue to fire at low rates and gaze may drift onward toward the target. It has been suggested that is one mechanism the saccadic system uses to correct the undershoot. Less pronounced drifts seen in humans may serve the same purpose. Short duration onward or backward post-saccadic drifts, often called glissades, are thought to be due to a mismatch between the neural signal that moves the eyes during a saccade (the saccadic burst) and that which holds the eyes in position after the saccade (the tonic signal). Small disconjugate glissades occur after saccades in normal subjects, but more prominent glissades can result from central (e.g., cerebellar or cortical) damage and from damage to the ocular motor nerves, muscles,

or orbital tissue. Finally, the recurring post-saccadic centripetal drift and inability to hold eccentric gaze (gaze-evoked nystagmus) that results from damage to the brainstem neural integrator is also a form of post-saccadic drift.

- Brainstem Burst Generator
- Oculomotor Dynamics
- Saccade, Saccadic Eye Movement
- Superior Colliculus

Postsurgical Pain

- Incisional/Postoperative Pain

Postsynaptic Currents (EPSCs and IPSCs) or Potentials (EPSPs and IPSPs)

Definition

By the patch clamp method, it is possible to record the electrical events occurring in a postsynaptic cell as a result of neurotransmitters' release by the presynaptic terminal and the consecutive opening of ionotropic receptors. In the "voltage clamp" mode, the voltage is kept constant, so it is possible to record the current passing through the open ion channels, called "postsynaptic current" (PSC). In the "current clamp" mode, it is possible to record the changes in membrane potential induced by the opening of ion channels, called "postsynaptic potentials" (PSP).

For an excitatory synapse, the binding of neurotransmitters induces the opening of cationic channels, which is depolarizing the cell. The induced electrical events are called "excitatory postsynaptic currents" (EPSCs) and "excitatory postsynaptic potentials" (EPSPs). For an inhibitory synapse, the binding of neurotransmitters induces the opening of chloride channels, which is hyperpolarizing the cell. The induced electrical events are called "inhibitory postsynaptic currents" (IPSCs), and "inhibitory postsynaptic potentials" (IPSPs).

- Patch Clamp
- Postsynaptic Potential

Postsynaptic Potential

MIYAKAWA, HIROYOSHI

Laboratory of Cellular Neurobiology, School of Life Sciences, Tokyo University of Pharmacy and Life Sciences, Tokyo, Japan

Definition

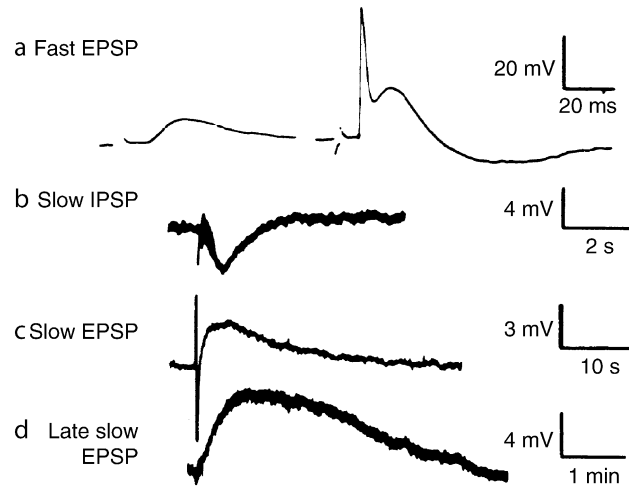
At chemical synapses, transmitter molecules are released from presynaptic terminals to the synaptic cleft or extracellular space as the mediator of transmission, and bind to receptors located on the membrane surface of postsynaptic cells. Binding of transmitters often give rise to transient change in the membrane potential of the postsynaptic cells, which is referred to as postsynaptic potentials (Fig. 1) [1–5]. In the case of electrical synapses [6], electric current flows directly from one cell to the other as the mediator of transmission, and causes a change in membrane potential. Although this can also be referred to as postsynaptic potential, the term "postsynaptic" is conditional, because the electrical synapses are bidirectional. Hence, this term is used mostly for chemical synapses.

Characteristics

Mechanisms for Generating Postsynaptic Potentials

Some types of receptors are directly coupled with ion channels while others are either indirectly coupled to ion channels or not coupled at all. Activation of the receptors, either directly or indirectly coupled to ion channels, gives rise to changes in the open probabilities of ion channels, which can be detected as the change in the ion conductance of the membrane. Depending upon the ion selectivity, ion conductance, composition of the ion species, and the membrane potential, electric current flows through ion channels and charges the membrane capacitance to generate postsynaptic potentials. The direction of the postsynaptic currents depends on the ion-selectivity of the ion-channels coupled to the receptors, the composition of the ion species that permeate through the ion-channels, and the membrane potential. The direction of the current reverses at a certain potential, when the membrane potential of the postsynaptic cell is varied (Fig. 2). This potential is called the reversal potential. For instance, the reversal potential of the nicotinic acetylcholine receptor is around zero mV in physiological conditions, and the reversal potential of GABA_A receptor is near the resting potential.

When the direction of the induced current is inward, and hence gives rise to depolarizing potential change, the current is referred to as excitatory postsynaptic current (EPSC), and the potential as excitatory postsynaptic potential (EPSP). When the direction of the



Postsynaptic Potential. Figure 1 Various postsynaptic potentials generated in frog sympathetic ganglion neurons. a: fast EPSP induced by stimulating preganglionic fibers. This potential is mediated by nicotinic acetylcholine receptors, which is coupled directly with ion channels. A stronger stimulation induces larger depolarization, which triggers action potential (right). b,c: slow IPSP and slow EPSP induced by repetitive stimulations. The slow IPSP and the EPSP are mediated by muscarinic acetylcholine receptors. d: A late slow EPSP evoked by repetitively stimulating spinal nerves is mediated by LHRH-like peptide. (Adapted from reference [7]).

current is outward and gives rise to hyperpolarizing potential change, the current is referred to as inhibitory postsynaptic current (IPSC), and the potential as inhibitory postsynaptic potential (IPSP).

Factors that Determine the Time Course of Postsynaptic Potentials

The time course of postsynaptic potentials range from a few milliseconds to a few minutes (Fig. 1). In general, fast postsynaptic potentials are mediated by ion-channel-coupled receptors (ionotropic receptors) for small molecule transmitters, and slow postsynaptic potentials are mediated by GTP-binding-protein-coupled receptors (metabotropic receptors). In the case of ion-channel-coupled receptors, channels open upon binding of transmitters, postsynaptic current flows through the channel, and the current charges the membrane to cause a change in the membrane potential (Fig. 3). Activation of GTP-binding-protein-coupled receptors usually generates second messengers in the cytoplasm, and the second messengers directly or indirectly regulate ion channels. Indirect regulation, in many cases, is by phosphorylation or dephosphorylation of ion channels.

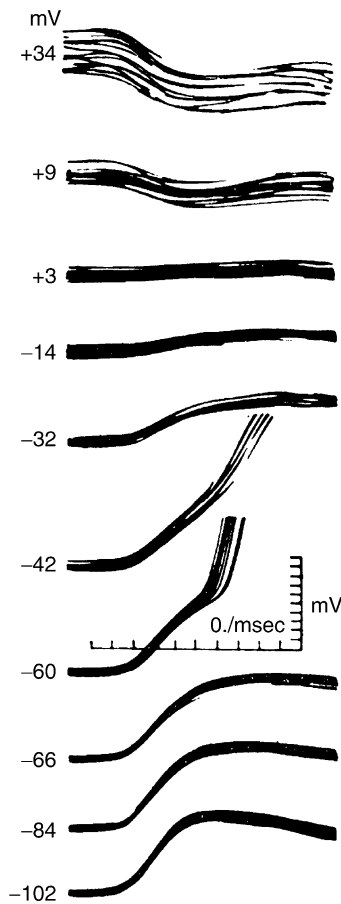
In excitable cells, action potentials can be triggered when the summation of postsynaptic potential provides enough depolarization. The amplitude and the time course of postsynaptic potentials are important in triggering action potentials. Many factors are involved in determining the amplitude and the time course of postsynaptic potentials. Some of the factors are the amount and the time course of transmitter release, the structure of synapses, the lifetime of transmitters in the synaptic cleft, the properties of postsynaptic

receptors, and the electrical properties of postsynaptic cells. The lifetime of transmitters in the synaptic cleft is determined by uptake mechanisms or degrading mechanisms, and estimated to be very short in the case of small molecule transmitters, such as glutamate and acetylcholine. The opening of channels indirectly linked to the receptors usually takes longer. The activation of ionotropic receptors is usually fast; hence, the rise time of postsynaptic currents is fast. The decay of postsynaptic currents also depends not only on the lifetime of transmitters in the cleft, but on the properties of receptors, channels, and the membrane as well. Some of the ligand-gated channels for small molecule transmitters show desensitization, and may be involved in determining the time course of postsynaptic potential. In the case of fast transmission, such as transmission at a neuromuscular junction, the decay time of postsynaptic potential is close to the time constant of the postsynaptic membrane, and is usually longer than that of the postsynaptic current (Fig. 3).

Dual whole cell recordings from neurons with long dendrites, such as neocortical pyramidal neurons, show that the postsynaptic potential measured from the cell body is slower compared to the potential measured near the input sites. This kind of distortion depends on the properties of the dendrites, and is important in determining cell response.

Higher Level Processes

The process of postsynaptic potential generation is part of ►synaptic transmission. Processes involved in synaptic transmission are classified as ►presynaptic processes, ►postsynaptic processes and the rest. The



Postsynaptic Potential. Figure 2 Reversal of Postsynaptic Potential. EPSP was measured from a cat motoneuron. The membrane potential was varied by injecting current through an intracellular electrode. The postsynaptic potential is depolarizing at potentials below 3 mV, and hyperpolarizing above 7 mV. Triggered action potentials are shown in the traces at -60 and -42 mV. (Adapted from reference [8]).

presynaptic processes are the processes concerning **transmitter release**, and the postsynaptic processes concerning **reception** of transmitters including the generation of postsynaptic potential. Upon reception of transmitters, the postsynaptic cells do not necessarily generate postsynaptic potential, but may activate intracellular signaling processes that include protein phosphorylation-dephosphorylation and protein synthesis through gene expression.

Lower Level Processes

- Diffusion of transmitters.
 - Activation and desensitization of postsynaptic receptors.
 - Charging and discharging of membrane capacitance by postsynaptic currents.

- Intracellular signaling.
- Clearance of transmitters from synaptic cleft.

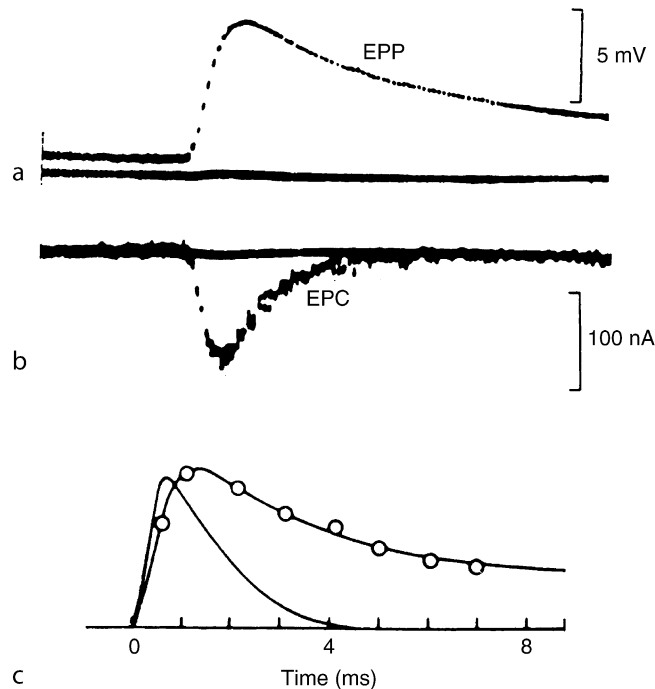
Process Regulation

Generation of postsynaptic potential is regulated by various ligands including biogenic amines, neuropeptides, and hormones. This kind of regulation is referred to as neuromodulation. The important mechanisms for neuromodulation are phosphorylation-dephosphorylation of proteins and gene expression of proteins, which take part in the generation of postsynaptic potential. The activities of the cells themselves, which take part in generating postsynaptic potentials, also regulate the process of postsynaptic potential generation. This kind of regulation is referred to as **neuronal plasticity**. Neuronal plasticity shares common mechanisms with neuromodulations, and is described elsewhere.

Function

To convey information for significant distance without decay, the neurons generate action potentials that propagate along the axonal processes. When the action potentials arrive at presynaptic terminals of chemical synapses, the information is converted into the form of chemical substances called transmitters. Upon reception of transmitters by the postsynaptic cells, the information is converted back to the form of electrical signal. The electrical signal can easily spread within the postsynaptic cell and can be summated and integrated to generate the output of the postsynaptic cells.

In the case of neuromuscular junctions, muscles receive a single presynaptic fiber. However, the amplitude of a postsynaptic potential (end-plate potential), induced by a single action potential in the presynaptic fiber, is large enough to trigger an action potential at the junction, which propagates along the entire length of the muscle fiber, and also into the transverse tubules, to induce a transient Ca rise and thereby generate a twitch response. The postsynaptic current generated by the activation of a postsynaptic receptor is greater than the current generated by the presynaptic action potential, and provide a current large enough to significantly depolarize the potential of the muscle membrane, the area of which is larger than that of the presynaptic membrane. Since the end-plate potential has large amplitude and a fast rate of rise, the muscle membrane can generate action potential. In contrast, most neurons in the central nervous system receive many thousands of inputs, and single synaptic inputs do not usually trigger action potentials in the postsynaptic cells because the amplitude of postsynaptic potentials is not large enough. Before an action potential is generated in the axons, many synaptic inputs need to be integrated. As synaptic inputs are converted into the form of an electrical signal, and electrical signals can quickly spread along the somato-dendritic axis, inputs



Postsynaptic Potential. Figure 3 Postsynaptic potential and current. a: End-plate potential (EPP) in a curarized frog muscle fiber. b: End-plate current (EPC) measured from the same fiber voltage-clamped at the resting potential. c: The continuous lines show the actual EPP and EPC. The circles show the EPP calculated from the EPC, assuming the time constant of the membrane to be 25 ms (adapted from reference [9]).

that arrive at various locations at various times can easily be summated and integrated. Thus, the postsynaptic potentials serve as mediators of information integration, which can lead to generation of action potentials in the postsynaptic cells that travel down the axon, and eventually induce transient Ca rise in the presynaptic terminals to trigger transmitter release.

There are cases in which the generation of action potential is skipped and postsynaptic potentials directly trigger transmitter release. In those cases, the extent of transmitter release depends on the amplitude of the potentials, and the synaptic transmission can be graded.

References

1. Cowan WM, Sudhof TG, Stevens CF (2001) Synapses. The Johns Hopkins University Press
2. Kuno M (1995) The synapse: function, plasticity, and neurotrophism. Oxford University Press, Oxford
3. Pappas GD, Purpura DP (ed) (1972) Structure and function of synapses. Raven, New York
4. Eccles JC (1964) The physiology of synapses," Springer-Verlag
5. Katz B (1996) "Nerve, Muscle, and Synapse," McGraw-Hill
6. Bennett MVL (2000) "Electrical synapses, a personal perspective (or history)." Brain Research Review 32:16–28
7. Kuffler SW (1980) Slow synaptic responses in the autonomic ganglia and the pursuit of a peptidergic transmitter. Journal of Experimental Biology 89:257–286
8. Coombs JS, Eccles JC, Fatt P (1955) Excitatory synaptic action in motoneurons. Journal of Physiology 130:374–395
9. Takeuchi A, Takeuchi N (1960) On the permeability of end-plate membrane during the action of transmitter. Journal of Physiology 154:52–67

Postsynaptic Receptor Trafficking

► Receptor Trafficking

Postsynaptic Receptors

Definition

Receptors that are expressed at the postsynaptic membrane and are responsible for mediating changes in the excitability of the postsynaptic cell.

► Synaptic Transmission: Model Systems

Posttetanic Potentiation

Definition

An increase in postsynaptic response to presynaptic release of neurotransmitter following a single stimulus that is applied at various times after a train of stimuli.

The cause is thought to be increased release of neurotransmitter from the presynaptic terminal.

- Force Potentiation in Skeletal Muscle
- Neuromuscular Junction

Posttraumatic Pain

- Incisional/Postoperative Pain

Posttraumatic Stress Disorder

Definition

A disorder that develops as a consequence of exposure to highly traumatic experiences, characterized by inappropriate fear responses to stimuli associated with those experiences.

- Learning and Extinction
- Stress

Postural Control

FAY B. HORAK

Neurological Sciences Institute, Oregon Health and Science University, Portland, OR, USA

Introduction

To inhabit the world, in all of its unpredictable, variable environments and situations, requires a powerful, yet flexible, system of postural control. For example, the ability to move from sitting to standing; to take a step; to respond to a slip or trip; to predict and avoid obstacles;

to carry a glass of wine without spilling it, even when walking across a rolling boat; and to orient your body to a speeding soccer ball, all require excellent postural control. Although neural control of postural orientation and equilibrium involves most of the nervous system and all body segments, the postural system is often forgotten because it usually operates at an automatic, non-voluntary level. Only after an injury to the nervous system or musculo-skeletal system, when we have to really “think about” our balance and postural alignment or battle dizziness and spatial disorientation, do we begin to appreciate the complex systems involved in postural control.

Biomechanical Goals of Postural Control

Postural control involves neural control of ►postural equilibrium and ►postural orientation [1]. Postural equilibrium involves coordination of sensory and motor ►strategies to maintain balance, that is, to stabilize the body’s ►center of mass over its ►base of support. An important goal of postural equilibrium control is to prevent falls during both self-initiated and externally-triggered disturbances of stability. The postural equilibrium system controls stability during stance posture as well as during locomotion and performance of voluntary tasks. Postural orientation involves the positioning of body alignment with respect to gravity, the support surface, visual environment and other ►sensory reference frames. The goals of postural equilibrium and postural orientation are independently controlled and sometimes subjects give up one goal for another. For example, an athlete may give up the goal of postural equilibrium in order to achieve their goal to orient their body appropriately to a ball.

Stance Posture

Although the musculoskeletal system affords some passive stability, humans and most animals require active postural muscle activation to maintain stance posture against gravity and to orient their body segments appropriately to their environment. To oppose the destabilizing effects of gravity, standing humans are continuously making small correction to upright body position, called ►postural sway. ►Postural muscle tone provides antigravity support and flexibly adjusts to changes in support, alignment, and environmental conditions [2]. Besides postural tone, control of postural sway requires integration of sensory information to detect body motion with respect to the environment and the activation of muscles to maintain equilibrium and alignment of segments. Postural sway during stance can be measured with ►stabilometry; quantification of forces under the feet as continuous displacement of the ►center of pressure [3]. Displacement of the center of pressure represents the combination of motion of the center of body mass as well as the

- ▶ **ground reaction forces** used to control the body
- ▶ **center of mass** over the base of foot support.

Several different types of ▶ **control theories** have been used to describe how the nervous system maintains consistent reference values for posture. Because posture is so adaptable and flexible, depending on the situation, models of human posture control include ▶ **optimal control** and ▶ **adaptive control**, such as ▶ **Kalman filters**, of more than one variable, such as position of center of body mass, orientation of the trunk and head in space, energy efficiency, etc. Postural sway during human stance is often modeled as an ▶ **inverted pendulum** biomechanical system in which the center of mass of the body is situated at the upper end of a rigid link that pivots about a joint at the base (i.e., the ankle), although actual body sway includes control of multiple segments.

Automatic Postural Responses

▶ **Automatic postural responses** counteract unexpected disturbances to equilibrium. In humans, postural responses are triggered at 100 ms in response to external perturbations. This latency of automatic postural responses is faster than the fastest voluntary postural reactions but slower than the fastest ▶ **stretch reflexes**. Stretch reflexes are triggered by muscle spindles and result in activation of the stretched muscles but these reflexes contribute little functional torque to correct postural equilibrium. Automatic postural responses include responses in muscles that are shortened, as well as stretched, as well as muscles far from the site of perturbation that can exert torque against surfaces to correct posture [4]. The recruitment of muscles in a postural response depends on the goal of maintaining equilibrium and not on stereotyped reflexes.

Automatic postural responses depend on ▶ **central set** so that they are specific to the conditions of support and adapt to prior experience. Central set is the readiness of the central nervous system for an upcoming event based on initial conditions, prior experience and expectations. For example, leg muscles are activated in response to surface perturbations during free stance but arm muscles are activated and leg muscles suppressed in response to surface perturbations when holding onto a stable support [5]. In addition, muscles on the back of the legs are activated in response to forward body sway while standing but muscles on the front of the legs and in the arms are active when supported on the hands and feet [6]. Postural responses change even in the first trial after a change in body configuration but continue to adapt with repeated trials to continue to optimize the response for the particular conditions. For example, a gradual adaptation of the postural response can be observed during repeated trials of surface rotation. In response to the first rotation, a destabilizing response may be seen in the stretched ankle extensor muscle but

with repeated rotations this activation of the extensor is suppressed and activation of the stabilizing ankle flexor gradually increases.

Subjects can also influence which postural response is selected and the magnitude of their response based on experience, expectations, and intention [7]. For example, the stretched ankle extensor muscle responses are inhibited and the shortened tibialis muscles are triggered when subjects are instructed to step in response to a forward body perturbation [8]. Poor coordination of automatic postural responses can result in failure to return to equilibrium in response to external perturbations. Automatic postural responses can be defined by their ▶ **postural strategies** and ▶ **postural synergies**.

Postural Strategies and Postural Synergies

Postural strategies can be defined by their functional goals and described based either on body kinematics (relationship of body segmental motion) or body kinetics (relationship of body segmental forces). Two main types of ▶ **postural movement strategies** can be used to return the human body to equilibrium when perturbed while standing: strategies that return the center of mass back over the ▶ **base of foot support** and strategies that change the base of support under the falling center of mass by stepping or reaching. The ▶ **fixed-support strategies**, that return the body center of mass over the base of foot support, form a continuum from the ankle strategy to the hip strategy. The ▶ **ankle strategy**, in which the body moves as a flexible inverted pendulum, is appropriate for small amounts of sway when standing on a firm surface [9]. ▶ **The hip strategy**, in which the body exerts torque at the hips to quickly move the body center of mass, is used when standing on surfaces not allowing adequate ankle torque or when the body center of mass must be moved more quickly such as for a faster, larger disturbance [9]. When subjects suddenly change from standing on a wide to a narrow surface, or vice versa, there is a gradual adaptation from an ankle to a hip strategy and vice versa with repeated perturbations. This gradual change in postural strategies suggest that they not only depend upon sensory feedback and current sensory conditions but also upon prior conditions based on central set.

▶ **Change-in-support strategies** of stepping and/or reaching to recover equilibrium in response to perturbations are also common, especially during gait and when it is not important to keep the feet in place [10]. However, even when subjects step in response to an external perturbation, they first attempt to return the body center of mass to the initial position by exerting angle torque. If a railing or other stable surface is available, subjects forced to extend their base of support by external displacement will also use a ▶ **reach-to-grasp** strategy [11]. Reaching reactions are initiated even faster than stepping reactions. Change-in-support

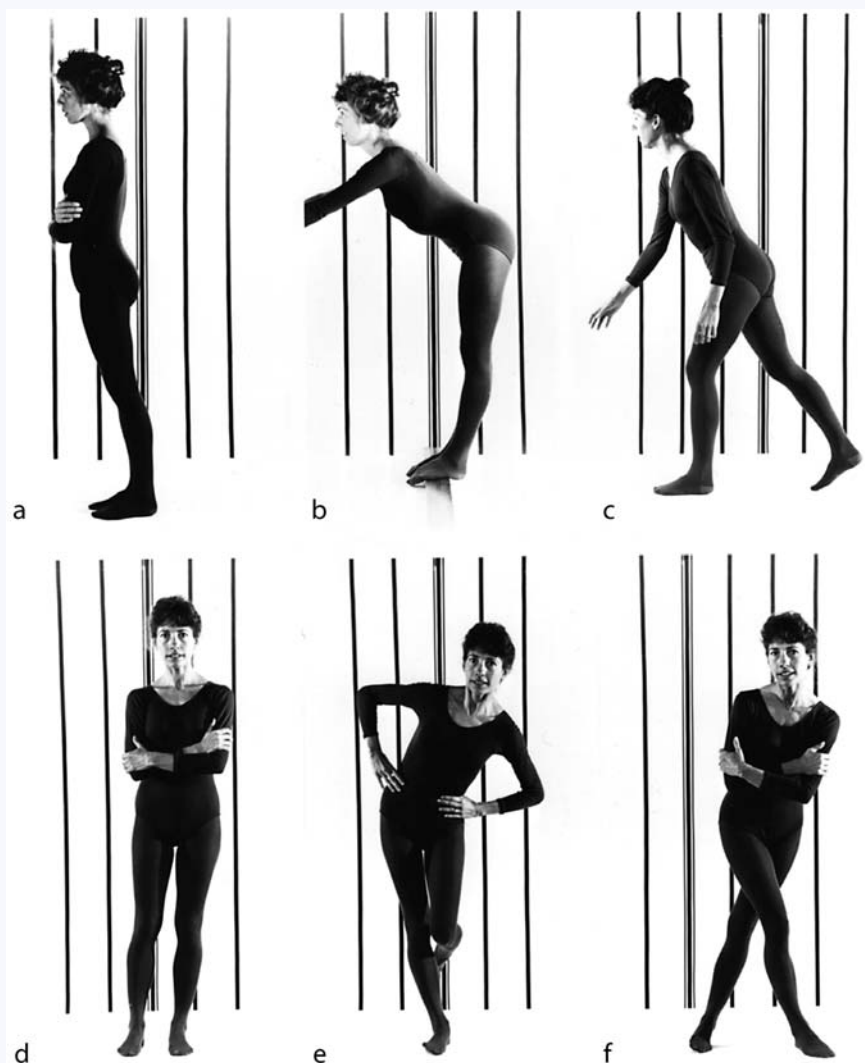
strategies are often used even under conditions in which it is biomechanically possible for subjects to return to equilibrium using a fixed-support strategy. **Figure 1** illustrates fixed-support and change-in-support strategies to correct forward and lateral postural displacements.

► **Postural synergies** are groups of muscles activated together by the nervous system to maintain equilibrium [4]. By eliminating the need to control each muscle independently, postural synergies are thought to simplify the neural control task of selecting and coordinating multiple muscles across the body. Postural synergies define the muscle activation patterns that are

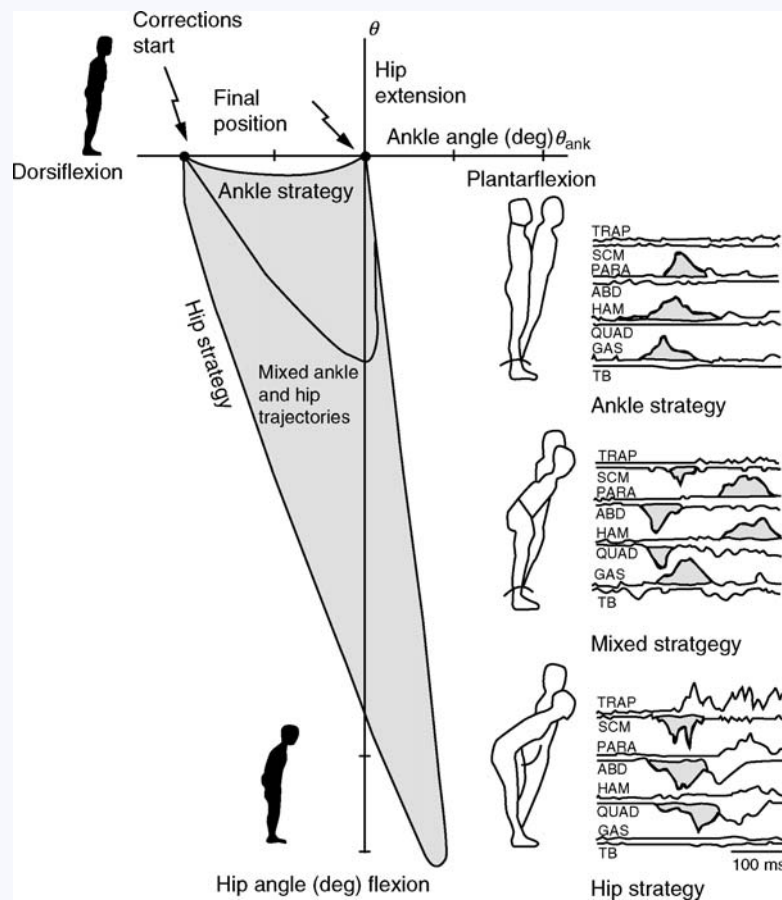
used by the nervous system to implement various postural strategies. For example, **Fig. 2** shows several muscles activated in the ankle, hip and mixed ankle-hip postural muscle synergies in response to forward sway perturbations.

Anticipatory Postural Adjustments

Voluntary movements are accompanied by ► **anticipatory postural adjustments** that act to counter, in a predictive manner, postural destabilization associated with a forthcoming movement [12]. Anticipatory postural adjustments are activated as ► **feedforward postural control**,



Postural Control. Figure 1 Shows examples of feet-in-place and stepping strategies to correct forward and lateral postural displacements. In response to small CoM displacements, humans use a strategy that maintains upright trunk orientation. In response to more forceful displacements, humans add rapid trunk and hip movements to move the CoM over the base of foot support. Stepping and reaching strategies can also be used to recover equilibrium by moving the base of support under the falling CoM. Lateral stepping includes both a cross-over strategy, as shown, and a step by the loaded leg to widen the stance width.



Postural Control. Figure 2 Plots the change in ankle and hip angles using the ankle and hip strategies and the continuum of mixed ankle-hip strategies used to return the body to upright stance equilibrium after a forward sway external perturbation.

prior to any sensory feedback indicating postural instability. For example, prior to taking a step, anticipatory postural adjustments move the body forward and onto the stance leg prior to lifting the stepping leg. In addition, when a standing subject rapidly moves their arms, leg and trunk muscles are activated more than 50 ms in advance of the prime mover arm muscles [13]. Anticipatory postural adjustments are specific to the biomechanical requirements of each specific movement and adapt when the biomechanical requirements change. For example, anticipatory postural adjustments in the legs associated with arm movements are reduced or disappear when subjects are supported at the trunk and no longer need the anticipatory postural muscle activity in the legs for stability [5]. These studies suggest that there is a preselection of an anticipatory postural muscle synergy associated with every voluntary movement requiring postural stability. This pre-selection or preparation of the sensorimotor nervous system in advance of movement has been called central set [14].

During locomotion, both anticipatory postural adjustments, via feedforward control, and automatic postural

responses, via feedback control, contribute to postural stability. Unperturbed walking or running in healthy individuals consists of placing the feet under a falling center of body mass so the nervous system must anticipate where the feet need to be to maintain equilibrium during walking [15]. During bipedal locomotion, the trunk segment and thus, the body center of mass, is inherently unstable in the lateral direction and thus requires frequent corrections of lateral trunk orientation and/or lateral foot placement. When an individual slips or trips or makes voluntary movements while walking or running, the same automatic postural strategies observed during stance (See *Postural Strategies*) are added to the locomotor pattern [16]. Somatosensory feedback is also used to modify joint stiffness and quick responses to accommodate unanticipated changes in surface configuration.

Sensory Integration

Sensory information from the ►**somatosensory, visual and vestibular systems** must be integrated in order to interpret complex sensory environments because

sensory information from a single sensory channel can be ambiguous and misleading. Postural control depends on the central neural interpretation of convergent sensory information from somatosensory, vestibular, visual systems. Thus, the nervous system controls posture via estimates of position and motion of the body and the environment by combining sensory inputs from several modalities. In addition, ►kinematic and ►kinetic body information must be integrated for control of posture. Sensory systems that signal kinematic position and motion of the body provide ►negative feedback control to minimize postural motion whereas sensory systems that signal kinetic force input provide ►positive feedback control to maximize joint torque when tilting [17]. Interpretation of sensory information by integrating sensory information across modalities is also thought to involve internal models of the body's sensory and motor dynamics, also called the body schema, as well as internal models of the environment. These internal models are based on expected sensory inputs from prior experience and provide the basis for central set. Errors between expected and actual sensory information is thought to be the basis for disorientation, dizziness, and motion sickness in both pathology and challenging environments.

Somatosensory inputs for posture include pressure information from skin in contact with surfaces, limb segment orientation from muscle proprioceptors and joint receptors, as well as muscle length, velocity and force information. Somatosensory inputs from many different types of peripheral sensory receptors converge onto neurons in the spinal cord to encode intersegmental and limb orientation in space [18]. Somatosensory inputs are important for triggering the earliest automatic postural responses in response to external perturbations. Thus, people with neuropathies that slow conduction of somatosensory inputs such as from diabetes or multiple sclerosis have longer than normal latencies of automatic postural responses. Somatosensory inputs are also important for providing information about the direction of perturbation and about the texture and stability of the support surface so that appropriate postural strategies can be selected. Somatosensory inputs can provide confusing, ambiguous information about body center of mass motion because they cannot distinguish between body motion over a stable surface and surface motion under a stable body, such as when standing on a moving boat or pier.

Vestibular inputs for posture are important for orientation of the trunk and head to gravity, especially when the surface is unstable. The vestibular system consists of two types of structures located in the inner ear, the ►labyrinths that encode head rotational acceleration and the ►otoliths that encode head linear acceleration, including gravity. The labyrinth consists of three, fluid-filled, semicircular canals that each sense

a different direction of head rotation via motion of hair cells imbedded in the ►cristae, the sensory tissue. Within the otoliths, the ►utricle senses horizontal linear acceleration such as during walking and the ►sacculle senses vertical acceleration such as during falling. Vestibulospinal inputs are particularly important for controlling orientation of the head and trunk in space but are not necessary to trigger automatic postural responses to external perturbations [19]. Vestibular inputs can provide confusing, ambiguous information about body center of mass motion because they cannot distinguish, on their own, between head motion over a stable body and head motion accompanying body center of mass motion. Vestibular information is thought to help the somatosensory system distinguish a stable from an unstable surface and then become increasingly important for controlling postural orientation the more unstable is the surface (see ►sensory re-weighting, below). Thus, patients who have lost all vestibular function can still stand and walk and show normal latencies of automatic postural responses to a slip or trip although they will orient to moving surfaces and become unstable when vision is not available [20].

Vestibular inputs must be interpreted via somatosensory inputs for the nervous system to control posture. For example, ►galvanic vestibular stimulation from direct current behind the ears can activate or inhibit the vestibular nerve and result in ►vestibulospinal responses. Vestibulospinal responses consist of medium latency activation of a group of muscles that tilt the body toward the side of the inhibited vestibular nerve when standing. The direction of body tilt depends on the direction the head is facing with respect to the base of foot support [21]. The muscles activated depend on which muscles can exert forces against the surface such that leg muscles are activated in free stance but arm muscles are activated with holding onto a stable surface [22]. Vestibular control of head orientation in space also depends on the close interaction between the vestibular and somatosensory systems via the ►vestibulocollic and ►cervico-collic reflexes.

Visual information provides knowledge of body sway and orientation in the environment and provides advanced information about potentially destabilizing situations. Vision can provide information about the direction and speed of body sway. For example, forward body sway is signaled by the visual system as backward visual flow across the peripheral retina and looming across the central retina. Visual information also allows perception and body orientation with respect to the vertical and horizontal visual environment (see perception of visual vertical, below). Thus, standing subjects exposed to slowly moving visual surrounds will sway with reference to the visual motion, even when unaware of it. Visual inputs can provide confusing, ambiguous information about body center of mass motion because

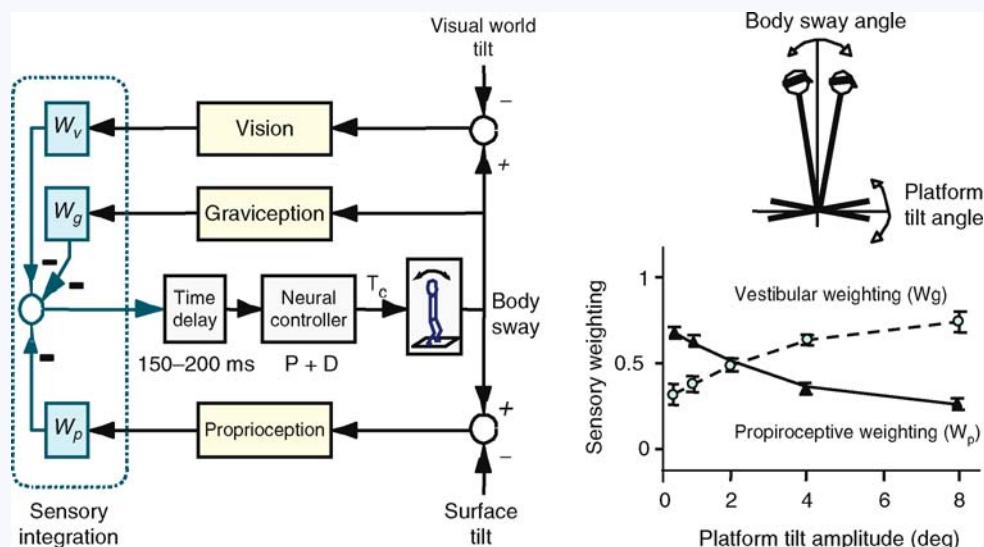
they, alone, cannot distinguish between body motion with respect to a stable visual surround and visual surround motion with respect to a stable body. For example, when stationary subjects view large moving scenes, especially in their peripheral vision, they often momentarily perceive self-motion in the opposite direction. When actually moving the body through space, vision also provides advanced, or ►**feedforward**, information to position body parts to avoid obstacles, navigate complex terrain, and plan motor strategies. For example, subjects tend to view obstacles in order to plan foot placement and clearance about 3 steps before they reach the obstacles [23].

The ability to orient the body with respect to gravity, the support surface, visual surround and internal references and to automatically alter how the body is oriented in space, depending on the context and task requirements is an important attribute of postural control. For example, a subject may automatically orient their body perpendicular to the support surface unless the support surface becomes unstable, when they will orient themselves to gravity or to their visual surround.

►**Sensory re-weighting** is an important mechanism for changing the relative contributions made by different sensory systems for postural control. Figure 3 shows a model of sensory integration for postural control in which somatosensory, vestibular and visual inputs can change weighting depending on changes in the environment. Using this model, studies have shown that in a well-lit environment with a firm base of support, healthy subjects rely on somatosensory 70%, vision 10% and vestibular 20% [20]. However, when healthy subjects stand on an unstable surface, they increase sensory weighting to vestibular and vision as

they decrease dependence on surface somatosensory inputs for postural orientation [24]. Ability to reweight sensory information depending on the sensory context is important for maintaining stability when moving from one sensory context to another, such as from a moving boat to firm ground. Individuals with loss of somatosensory, vestibular or visual input from pathology are limited in their ability to reweight postural sensory dependence and thus, are at risk of falls in particular sensory contexts. In addition, some central nervous system disorders may impair the ability to quickly reweight sensory dependence, even when the peripheral sensory systems are intact. Subjects can use ►**sensory substitution** to replace one sensory modality for another to help control posture. For example, light touch on a cane can be used to substitute haptic sensory cues for missing vestibular or somatosensory inputs due to pathology and thereby reduce postural sway in stance [25,26]. Biofeedback systems that provide visual, auditory or somatosensory inputs to the nervous system correlated with body sway have also been shown to provide effective sensory substitution to improve postural stability in patients with loss of sensory information.

Healthy individuals also have a conscious perception of vertical spatial orientation. ►**Perception of verticality**, or upright, may have multiple neural representations [27]. In fact, ►**perception of visual vertical**, or ability to align a line in the dark with gravity, is independent of ►**perception of postural (or proprioceptive) vertical**, or ability to align the body in space without vision [28]. For example, the internal representation of visual, but not postural, vertical is tilted in subjects with unilateral vestibular loss, whereas the internal representation of



Postural Control. Figure 3

postural, but not visual vertical is tilted in some subjects with stroke. A tilted or inaccurate internal representation of vertical will result in automatic postural alignment that is not aligned with gravity.

Neuroanatomy of Posture Control and Clinical Implications

Control of posture is distributed in the nervous system and the musculoskeletal system such that pathology almost anywhere in the nervous system or musculoskeletal system can impair postural equilibrium and/or postural orientation. The spinal cord is sufficient for maintaining antigravity support and locomotor patterns but not for maintaining balance [29]. Sensory pathways in the spinal cord carry somatosensory information about limb orientation as well as motor pathways such as the medially located vestibulospinal and reticulospinal pathways for activating postural muscle synergies. In the brainstem, the vestibular nuclei are important for integrating sensory information across modalities for postural orientation and the reticular formation is likely involved in organizing postural synergies. The important **►role of the cerebellum** in posture can be seen by the severe problems with postural stability and postural orientation in patients with damage to the cerebellum. Damage to the spinocerebellum, specifically, impairs postural stability by causing larger than normal automatic and anticipatory postural adjustments and by impairing the ability to optimize postural strategies based on prior experience [30]. In contrast, damage to the vestibulocerebellum results in difficulty using vestibular or visual information to orient the body with reference to gravity or visual references. The basal ganglia's importance to postural control can be seen by the frequent falls in patients with pathology involving the basal ganglia, such as Parkinson's disease. The basal ganglia is important for quickly changing postural strategies when conditions change, for regulating postural muscle tone, for generating forceful anticipatory and reactive postural responses and for perception of postural orientation [31]. The cerebral cortex is involved in postural control in as many complex ways as voluntary movement [32]. The cortex is involved in changing postural responses with alterations in cognitive state, initial sensory-motor conditions, prior experience, and prior warning of a perturbation, all representing changes in central set. In addition, the supplementary motor cortex is involved in generating anticipatory postural adjustments and the primary motor cortex participates in longer latency postural responses to perturbations. Parietal and temporal association cortical areas are involved in perception of spatial orientation and in formulating the internal models of the body and the environment so important to postural control. Thus, damage to almost any part of the cortex from a cerebral vascular accident can impact postural stability or orientation.

References

- Horak FB, Macpherson JM (1996) Postural orientation and equilibrium. In: Rowell LB, Shepherd JT (eds) *Handbook of physiology. Exercise: regulation and integration of multiple systems*. Oxford University Press, New York, 255–292
- Gurfinkel V, Cacciatore TW, Cordo P, Horak F, Nutt J, Skoss R (2006) Postural muscle tone in the body axis of healthy humans. *J Neurophysiol* 96(5):2678–87
- Chiari L, Rocchi L et al. (2002) Stabilometric parameters are affected by anthropometry and foot placement. *Clin Biomech* 17(9–10):666–77
- Ting LH, Macpherson JM (2005) A limited set of muscle synergies for force control during a postural task. *J Neurophysiol* 93:609–613
- Cordo PJ, Nashner LM (1982) Properties of postural adjustments associated with rapid arm movements. *J Neurophysiol* 47:287–302
- Macpherson JM, Horak FB et al. (1989) Stance dependence of automatic postural adjustments in humans. *Exp Brain Res* 78:557–566
- Horak F, Kuo A (eds) (2000) *Postural adaptation for altered environments, tasks, and intentions. Biomechanics and neural control of posture and movement*. Springer, New York
- Burleigh AL, Horak FB (1994) Influence of prior experience and instruction on postural organization of perturbed step initiation. *Soc Neurosci Abstr* 20:794
- Horak FB, Nashner LM (1986) Central programming of postural movements: adaptation to altered support-surface configurations. *J Neurophysiol* 55(6):1369–1381
- Maki BE, McIlroy WE (1997) The role of limb movements in maintaining upright stance: the “change-in-support” strategy. *Phys Therapy* 77:488–507
- McIlroy WE, Maki BE (1995) Early activation of arm muscles follows external perturbation of upright stance. *Neurosci Lett* 184:1–4
- Massion J (1992) Movement, posture and equilibrium: interaction and coordination. *Prog Neurobiol* 38:35–56
- Belenkii VY, Gurfinkel VS et al. (1967) Elements of control of voluntary movements. *Biofizika* 12:135–141
- Prochazka A (1989) Sensorimotor gain control: a basic strategy of motor systems? *Prog Neurobiol* 33:281–307
- Winter DA, Patla AE et al. (1990) Assessment of balance control in humans. *Med Prog Technol* 16:31–51
- Nashner LM, Forssberg H (1986) Phase-dependent organization of postural adjustments associated with arm movements while walking. *J Neurophysiol* 55(6):1382–1394
- Mergner T, Maurer C et al. (2002) Sensory contributions to the control of stance: a posture control model. *Adv Exp Med Biol* 508:147–152
- Bosco G, Poppele RE (1997) Representation of multiple kinematic parameters of the cat hindlimb in spinocerebellar activity. *J Neurophysiol* 78(3):1421–1432
- Mergner T (2002) The matryoshka dolls principle in human dynamic behavior in space: a theory of linked references for multisensory perception and control of action. *Curr Psychol Cogn* 21(2–3):129–122
- Peterka RJ, Benolken (2002) Sensorimotor integration in human postural control. *J Neurophysiol* 88(3):1097–1118
- Lund S, Broberg C (1983) Effects of different head positions on postural sway in man induced by a

reproducible vestibular error signal. *Acta Physiologica Scandinavica* 117:307–309

22. Storper IS, Honrubia V (1992) Is human galvanically induced triceps surae electromyogram a vestibulospinal reflex response? *Otolaryngol Head Neck Surg* 107:527–535
23. Patla AE (1992) The neural control of locomotion. 1–36
24. Peterka RJ, Loughlin PJ (2004) Dynamic regulation of sensorimotor integration in human postural control. *J Neurophysiol* 91(1):410–423
25. Creath R, Kiemel T et al. (2002) Limited control strategies with the loss of vestibular function. *Exp Brain Res* 145(3):323–333
26. Dickstein R, Peterka R et al. (2003) Effects of light fingertip touch on postural responses in subjects with diabetic neuropathy. *J Neurol Neurosurg Psychiatry* 74:620–626
27. Karnath HO, Fetter M et al. (1998) Disentangling gravitational, environmental, and egocentric reference frames in spatial neglect. *J Cogn Neurosci* 10(6):680–690
28. Anastasopoulos D, Haslwanter T et al. (1997) Dissociation between the perception of body verticality and the visual vertical in acute peripheral vestibular disorders in humans. *Neurosci Lett* 233(2–3):151–153
29. Macpherson JM, Fung J (1999) Weight support and balance stance in the chronic spinal cat. *J Neurophysiol* 82(6):3066–3081
30. Horak FB, Diener HC (1994) Cerebellar control of postural scaling and central set in stance. *J Neurophysiol* 72(2):479–493
31. Horak FB, Frank J et al. (1996) Effects of dopamine on postural control in parkinsonian subjects: scaling, set and tone. *J Neurophysiol* 75(6):2380–2396
32. Jacobs JV, Horak FB (2007) Cortical control of postural responses. *J Neural Transm* 114(10):1339–1348

Postural Equilibrium

Definition

A state in which the body is either at rest, moving at constant velocity or executing a repeatable (periodic) pattern of motion. A stable system is one that returns to a state of equilibrium after it has been perturbed.

► Postural Strategies

Postural Instability

Definition

Impairment of balance when standing, walking, or turning.

Postural Muscle Tone

VICTOR S. GURFINKEL

Neurological Sciences Institute, Oregon Health & Science University, Portland, OR, USA

Definition

Postural tone is the steady contraction of muscles that are necessary to hold different parts of the skeleton in proper relation to the various and constantly changing attitudes and postures of the body.

Description of the Theory

Decerebrate Posture

Because postural muscle tone is completely suppressed by narcosis, postural tone has mainly been studied using an experimental model called the decerebrate animal [1]. In the decerebration of mammals, the cerebral cortex and thalamus are surgically inactivated by intercollicular cross-section of the brain stem under general anesthesia. Once the effects of the anesthesia have dissipated, the condition known as “decerebrate rigidity” can be seen. This condition is characterized by a strong extended neck, trunk, tail and limbs, which resist attempts to flex them. In decerebrate rigidity, there is no sensation of pain. Because of this rigidity, when the decerebrate cat is placed on its four limbs, tension in the limb muscles is enough to maintain its body posture. This muscle tone has been named “postural tone” [1]. In decerebrate animals, the neuronal structures of the brain stem and spinal cord are in an active condition. Therefore, this model is useful for studying many questions of neurophysiology. For example, on a background of high muscle tone, it is possible to study not only influences of excitation, leading to the enhancement of muscle tone, but also to study inhibition, which results in the suppression of muscle tone.

In the past, many researchers have been devoted to studying the nature of decerebrate rigidity. It was found that deafferentation (i.e., sectioning appropriate dorsal roots) abolishes decerebrate rigidity of limb muscles [1]. In addition, it was found that the tonus of the extensor muscles is autogenous, in that each muscle is dependent on afferent nerve fibers from the muscle itself (“myotatic component” in decerebrate rigidity). These findings were reproduced many times [2]. This showed that the origin of decerebrate rigidity cannot be completely explained by the myotatic component. The actual situation is more complex. In studies of decerebrate cats, it was shown that in addition to proprioception, there are other sources of postural tonic activity that are connected to the position of the head

in space and the position of the head relative to the trunk [3]. These neck and vestibular tonic reflexes strongly influence the level of decerebrate rigidity and cause a redistribution of muscle tension.

Another type of experiment elucidated mechanisms of decerebrate rigidity. This experiment involved, as described above, the cutting of the dorsal roots to the forelimbs in a decerebrate preparation to make forelimbs flaccid. When the spinal cord was transected below the level of origin of the brachial nerves (postbrachial transection), the forelegs became rigid, although still deafferented. This effect can be explained by the fact that post-brachial transection of the spinal cord cuts off the flow of inhibitory pulses to the motoneurons that ascend from tonically active propriospinal neurons located in L2–L3 segments (the “Schiff-Sherrington inhibition”).

It is known that the cerebellum is involved in the control of muscle tone and that damage to the cerebellum is accompanied by a reduction in tone. However, it has been shown that the removal of the cerebellum in a cat that has undergone intercollicular brain stem transection increases decerebrate rigidity. This same effect can be caused by bilateral destruction of the fastigial nuclei. Here again, rigidity returns to the deafferented forelimbs of the decerebrate preparation.

Another model of decerebrate rigidity involves properties that are different from the intercollicular preparation and has extended our knowledge about the mechanisms involved in decerebrate rigidity. It is the so-called anemic decerebration (high ligation of the basilar artery and of both carotids) that functionally inactivates all the nervous structures that are supplied by blood vessels arising cephalad to the basilar ligature, including the anterior lobe of cerebellum. After anemic decerebration, strong tension in all extensor muscles also develops. However, decerebrate rigidity, after anemic decerebration, is not eliminated by transection of the dorsal roots. In the anemic preparation, rigidity is caused by the nonmyotatic component of muscle tension, represented mainly by the tonic labyrinthine influences on the spinal motoneurons. The nonmyotatic component of extensor rigidity is released by anemic damage to the anterior lobe of the cerebellum.

One cogent interpretation of the evolution of the cerebellar regulation of postural tone is that postural extensor mechanisms are tonically inhibited through bulbospinal relays by the paleocerebellum, whereas a tonic facilitating influence is exercised by the neocerebellum on the cerebral cortex [2]. After efferent innervation (γ innervation) of muscle spindles was established, intercollicular decerebrate rigidity was called “ γ rigidity,” and anemic rigidity was called “ α rigidity” [4]. A comparison of these two kinds of decerebrate rigidity showed that they change differently under the influence of various factors, suggesting that both

muscle and labyrinthine receptors tonically support extensor rigidity. The disappearance of decerebrate rigidity following deafferentation indicated that in the intercollicular animal, the vestibular component is tonically inhibited by cerebellar and spinal mechanisms (Schiff-Sherrington). However, in anemic decerebrate animals, the importance of the myotatic component of decerebrate rigidity is reduced by γ paralysis, while that of the vestibular component is increased through a release mechanism. It is possible that other brain structures also participate in the formation of decerebrate rigidity. The posture of the decerebrate animal may be the consequence of a disturbance in balance between different sources of tonic excitatory and inhibitory influences.

Postural Adaptation

As mentioned above, a decerebrate cat can be stood on its legs and will maintain this position; a position that is a caricature not only because the cat's legs are hyper-extended but also because the body is absolutely motionless due to constant muscle tension. Such immobility can also be observed naturally in intact animals (e.g., a hunting dog becomes motionless when pointing to detected game, rabbits experience immobilization catatonia when faced with danger and many animals undergo hypnosis). However, immobilization, that is muscles in a state of constant tension, is the exception not the rule. Postural tone of muscles ranges from very high tension at exaggerated decerebrate rigidity, up to complete atonia in the vertebra prominens reflex. Although the decerebrate animal exhibits rigidity, it still has the capacity to adapt to experimental conditions. In 1909, it was shown for the first time that when a decerebrate animal's limb was flexed, the limb did not move back to its initial position; rather it adapted and maintained the new position [5]. This condition was explained as: “The forced stretch causes a relaxation of the tonic extensor, and this condition of relaxed tonus persists after the forced stretch itself has ceased. This reaction, may for brevity, be termed the ‘lengthening reaction’” [5]. Similarly, when a decerebrate animal's limb is moved, the antagonist muscles shorten and adapt to their shorter length. In this shortening, the muscle insertion and origin are brought closer together, which appears to induce heightened tonus in the muscle—a reaction that has been termed the “shortening reaction” [5]. In other words, the limb that is brought by movement into a new posture remains in that new posture when released. This property is especially present in skeletal muscles when the nerve centers are operating to maintain posture [5]. Such behavior of tonically active muscles has been termed “plasticity.” Skeletal muscles in this form of reflex contraction quite readily adapt themselves to different lengths while counteracting one and the same load [6].

The shortening reaction can be observed in humans. In some neurological diseases that are accompanied by tone abnormalities, passive movement of a joint results in the contraction of shortened muscles. This contraction is tonic, that is, it persists after the movement terminates.

Another form of postural tone adaptation in decerebrate animals deals with neck and vestibular tonic reflexes [3]. In decerebrate animals, neck reflexes result in a redistribution of tonic muscle tension that is dependent on the relative position of the head and trunk. Dorsiflexion of the neck produces extension of forelimbs and flexion of hind limbs, ventriflexion of the neck produces flexion of the forelimbs and extension of the hind limbs, lateral flexion of the neck (ear toward the shoulder) produces extension of the fore and hind limbs on the side toward which the head is turned and rotation of the head on the neck produces extension of both the fore and hind limbs on the side toward which the chin is turned. The changed distribution of muscle tonus in the limbs continues as long as the head retains a specific relationship to the trunk. Changes in head position in space when neck reflexes are inactivated, also result in a redistribution of postural tone of neck, trunk and legs muscles. There is one position of the head in space in which the extensor tone of the limbs is maximal and one position of the head in space in which it is minimal. The maximal and minimal positions differ from each other by 180°. When the position of the head in space is changed when the body is in different positions, tonic neck and labyrinth reflexes combine to modify postural tone in various ways.

Another factor that influences the distribution of postural tone is how the body or limbs contact the support surface. When a limb contacts the support surface, dorsiflexion occurs in the distal part of the limb (fingers and hands, toes and feet), which results in significant enhancement (strengthening) of tone in the extensor muscles of all joints in the limb (termed “the positive reaction of support”). The limb, in this enhanced tonic state, is capable of maintaining body weight. This reaction has been observed in animals without a cerebellum [7]. In decerebrate animals, this reaction is more difficult to observe because the limbs are in an initial state of high tonic tension. This type of reaction has also been observed in humans with brain pathology. In the examples discussed above, the adaptive changes of postural tone were tonic in character, but in natural conditions, adaptive changes are also phasic in character. In natural conditions, such reactions are mainly directed to preserving balance and maintaining the stability of body parts during movement. Almost all movements of the hands and legs in natural conditions inevitably require a redistribution of postural tone. For example, when a human moves the arms to catch a falling object, contact with the object

is preceded by the contraction of appropriate hand muscles. Similarly, when a human moves a leg when taking a step, this movement is preceded by a change in muscle tone distribution in the trunk and in the opposite leg. Adaptation of muscle tonic activity maintains harmony between mobility and stability.

References

1. Sherrington CS (1898) Decerebrate rigidity and reflex coordination of movements. *J Physiol* 22:319–332
2. Bremer F (1932) Le tonus musculaire. *Ergebn d Physiol* 34:678–740
3. Magnus R, de Kleijn A (1912) Die Abhängigkeit des Tonus der Extremitätenmuskeln von der Kopfstellung. *Arch f d ges Physiol* 145:455–548
4. Granit R (1955) Receptors and sensory perception. Yale University Press, New Haven
5. Sherrington CS (1909) On plastic tonus and proprioceptive reflexes. *Quart J Exper Physiol* 2:109–156
6. Sherrington CS (1915) Postural activity of muscle and nerve. *Brain* 38:191–234
7. Rademaker GGJ (1931) Das Stehen: Statische Reaktionen, Gleichgewichtreaktionen und Muskeltonus unter besonderer Berücksichtigung ihres Verhaltens bei kleihirlosen Tieren. Springer, Berlin Heidelberg New York

Postural Orientation

Definition

Postural orientation refers to the positioning of the body or body segments with respect to some reference frame.

The selection of the reference frame is arbitrary and there are many choices. A commonly used and often implicit reference is a global or earth fixed reference frame. Other common reference frames include clinical joint based frames where joint motions can be described, for example in terms of extension or flexion and local reference frames which might move with the body or be affixed to a particular body segment.

► Posture – Sensory Integration

Postural Reactions

► Postural Strategies

Postural Strategies

BRIAN E. MAKI

Centre for Studies in Aging, Sunnybrook and Health Sciences Centre, University of Toronto, Toronto, Canada

Synonyms

Balance-recovery reactions; Postural reactions; Postural synergies

Definition

Postural strategies are specific patterns of muscle activation, joint torque, joint rotation and/or limb movement that are evoked by balance perturbation. These reactions serve to prevent the body from falling and act to re-establish a state of **postural equilibrium**. Triggered by multiple sensory inputs, they involve polysynaptic spinal and supraspinal neural pathways and are highly adaptable to meet functional demands. Strategy selection and modulation are dependent on: (i) the features of the perturbation (timing, direction, magnitude, predictability), (ii) the **central set** of the individual (affect, arousal, attention, expectations, prior experience), (iii) ongoing activity (cognitive or motor) and (iv) environmental constraints (on reaction force generation and limb movement).

Description of the Theory

Biomechanical Requirements for Postural Equilibrium

The mechanics of the upright human body can be modeled as a multi-link **inverted pendulum**, with each link corresponding to a body segment (e.g., foot, shank, thigh, trunk) [1]. Static postural equilibrium requires the **center of mass (COM)** of this linkage to be positioned over the **base of support (BOS)**; however, the linkage is inherently unstable, due to the force of gravity. Additional destabilizing forces arise due to movement of the body and interaction with the environment. The BOS is usually defined by the position of the feet, but may include the arms when grasping or touching an object for support. In the absence of arm support, static equilibrium requires the COM to be positioned over the feet and the perimeter of this foot area can be considered to represent the static stability limits associated with the BOS. Dynamic equilibrium takes into account the additional requirement of controlling the momentum associated with movement of the COM [2]. If the COM is moving with sufficient horizontal velocity, it is possible for the body to be dynamically unstable, even when the COM is positioned over the BOS. Conversely, it is possible for the body to be dynamically stable even though the COM is located outside the static stability limits of the BOS, provided that the COM is moving

toward the BOS with sufficient velocity that it can eventually be repositioned over the BOS.

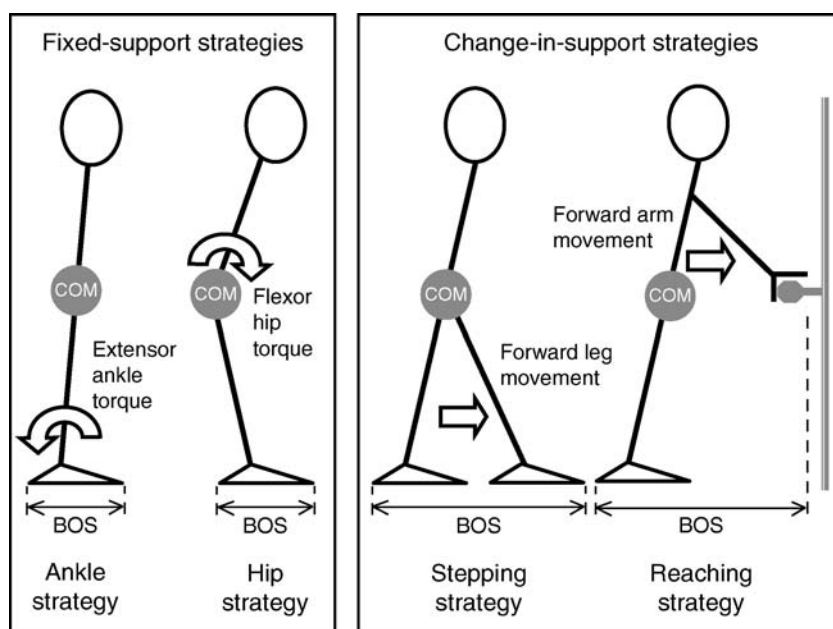
Postural Strategies for Responding to Perturbation

Passive muscle stiffness could, in theory, be sufficient to maintain a stable upright posture under static conditions; however, the reality is that coordinated muscle activation is required to keep the body upright in the activities of daily life. To maintain upright stance, the central nervous system (CNS) must actively regulate the static and dynamic relationship between the COM and the BOS [2]. Responses to perturbations must involve deceleration of the COM, but can also involve changes in the BOS. Accordingly there are two distinct classes of postural strategies: (i) **fixed-support** (“feet-in-place”) strategies, in which the BOS is not altered and (ii) **change-in-support** reactions, where the BOS is altered via rapid **stepping** or reaching movements of the limbs [3]. See Fig. 1.

Although the focus here is on reactions to perturbation of stance, it should be noted that fixed support and change-in-support reactions are also used to respond to perturbations experienced during gait. However, the gait responses may show some differences, e.g., bilateral asymmetries in muscle activation, phase dependent gating of sensory inflow and triggering of additional strategies (e.g., elevation of the swing foot in response to a trip perturbation). In addition, stepping reactions during gait may involve modulation of an ongoing step, while arm reactions may be affected by gait-related arm swing.

Postural reactions can be controlled, to some extent, in a predictive manner provided that the characteristics of the destabilization are known in advance (e.g., the **anticipatory postural adjustments** that normally precede preplanned volitional movement or the reactions evoked by a periodic sinusoidal perturbation). In general, however, sensory information about the body orientation and motion is also required, particularly when balance is disturbed unexpectedly by a sudden perturbation (e.g., due to a force applied to the body or motion of the support surface). This sensory information is used to detect instability and to generate appropriate stabilizing responses, either by triggering and scaling preprogrammed “feedforward” reactions or by continuously updating ongoing “feedback” corrections. The initial phases of the reactions to sudden, transient perturbation are thought to be triggered feedforward corrections, whereas the later phases may also involve ongoing feedback control.

Postural strategies involve multiple sensory inputs (somatosensory, vestibular, visual) and highly adaptable triggered reactions, rather than stereotyped short-latency reflexive responses arising primarily from a single source of afferent drive (e.g., vestibulo-spinal reflex, myogenic stretch reflex). The triggering afferent signals depend on the nature of the perturbation, e.g., whether the



Postural Strategies. Figure 1 Postural strategies. Static postural equilibrium requires the body center of mass (COM) to be positioned over the base of support (BOS). The *stick figures* illustrate potential responses evoked by a perturbation that induces forward falling motion of the COM. Note the large increase in BOS associated with the change-in-support strategies.

perturbation involves the movement of the support surface or a force applied to the upper body. Responses to support surface perturbations may involve ankle muscle spindles (Ia afferents); however, the role of the vestibular system and/or somatosensory inputs from other joints cannot be ruled out [4] and it appears that even visual inputs (which are generally thought to require much longer processing times) can modulate the earliest postural muscle activation in some situations. The earliest muscle activation associated with the postural reaction typically occurs at a latency of about 80 to 140 ms after perturbation onset.

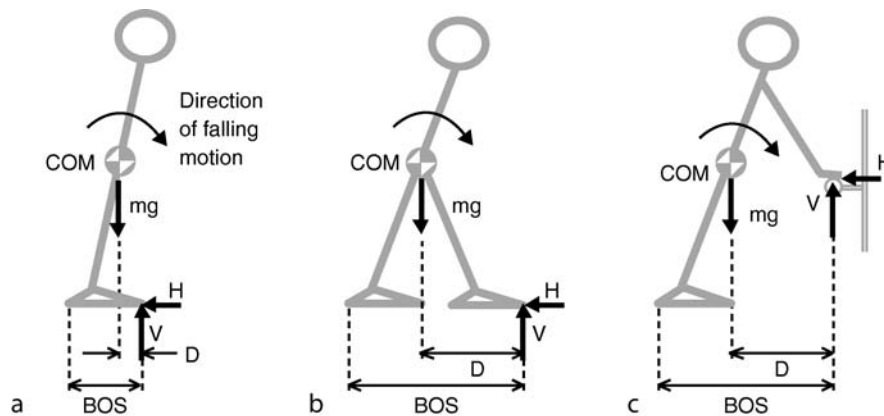
The control of these reactions is mediated via polysynaptic spinal and supraspinal neural pathways [5]. Furthermore, although balance reactions are often considered to be “automatic,” it appears that control of later phases of the response (e.g., 200 to 500 ms after perturbation onset) may involve transcortical pathways and high-level cognitive and attentional systems [6]. This is supported by evidence from dual-task studies, where later phases of the balance response can be affected by performance of a concurrent cognitive task. Measurements of perturbation-evoked cortical potentials also support cognitive involvement. Thus, it appears that reactions to perturbation are not as stereotyped as once believed, but are in fact highly adaptable to the functional demands of maintaining stability, i.e., regulating the relationship between COM and BOS. Although some researchers have speculated that critical afferent information for determining the state of the COM may arise from

load receptors such as Golgi tendon organs, maintaining stability also requires information about the state of the BOS and the direction of a gravitational reference vector. In contrast to the traditional view that the vestibular otoliths provide the reference vector, some researchers have suggested a construct based on multiple sensory modalities. Determination of the BOS state is also probably dependent on multiple sensory inputs, although it appears that the plantar cutaneous mechanoreceptors may play a particularly critical role in providing information pertaining to BOS stability limits and the state of contact between foot and ground [1].

Fixed-Support (Feet-in-Place) Strategies

In ►**fixed-support strategies**, the COM motion that is induced by the postural perturbation is decelerated via generation of active muscle torques at the joints of the supporting leg or legs, as well as the trunk and upper limbs. These joint torques create antero-posterior “environment reaction” forces (i.e., shear force at the foot ground interface, as well as forces occurring at the hand if it is in contact with a stable object or surface) and it is these forces that act to decelerate and arrest the horizontal COM motion (Fig. 2). Fixed-support reactions occur very rapidly (e.g., onset latency of 80 to 140 ms in ankle muscles) and are essentially the first line of defense against postural perturbation.

Biomechanically, the upright human body has redundant degrees of freedom. This means that there are potentially many different combinations of muscle



Postural Strategies. Figure 2 Biomechanical advantages of change-in-support strategies (*panels b and c*) in comparison to fixed-support strategies (*panel a*). The postural reaction must generate a horizontal ground-reaction shear force (H) in order to decelerate the horizontal motion of the center of mass (COM). Note that the stepping (*b*) and grasping (*c*) reactions can greatly amplify the moment arm (D) between the COM and the contact force (V), which allows greater shear force to be generated (H is approximately proportional to D). In addition, the increase in base of support (BOS) allows a larger range of COM motion to be accommodated without loss of stability. Adapted from [1].

torques at the various joints that could be used to re-establish postural equilibrium, in responding to a given postural perturbation. It has been proposed that the CNS deals with this redundancy, and simplifies the control problem, by restricting the response to a finite number of specific response patterns (often referred to as synergies as well as strategies) or weighted combinations of these patterns.

Early research identified two major strategies for responding to antero-posterior perturbations: (i) the [ankle strategy](#) and (ii) the [hip strategy](#) [7]. Although not included in the original definitions of these strategies, activation of knee muscles can also play an important role in both ankle and hip strategies, particular for perturbations that induce a backward falling motion and hence tend to cause the knee to “collapse” in flexion [4].

In the ankle strategy, the predominant stabilizing action involves active generation of ankle torque. This strategy is characterized by activation of ventral muscles (i.e., ankle dorsiflexors, hip flexors, abdominals) in response to backward falling motion and activation of dorsal muscles (i.e., ankle plantarflexors, hip extensors, paraspinals) in response to forward falling motion. In essence, the body is controlled to behave predominantly in the manner of a single-link inverted pendulum, with joint rotation primarily occurring at the ankle. For responses to support-surface perturbations, the involved muscles fire in a distal to proximal sequence.

In the hip strategy, the predominant stabilizing action involves active generation of hip torque. This strategy is characterized by activation of muscles on the opposite side of the thigh and trunk in comparison to the ankle strategy, i.e., dorsal muscles in response to backward

falling motion and ventral muscles in response to forward falling motion. There is relatively little activation at the ankle. The main effect biomechanically is to generate stabilizing shear force (at the foot ground interface) that is larger than the shear force that can be generated using the ankle strategy.

The ankle strategy predominates at small levels of perturbation, whereas increasing levels of hip activation are added as the postural challenge increases [8]. These latter “mixed strategy” responses were originally thought to involve a weighted combination of the ankle and hip strategies; however, the “pure” hip strategy is seldom if ever observed during natural behavior (in experiments, it was learned over the course of repeated trials that involved standing on a shortened support surface, which limited ability to generate stabilizing ankle torque) [3]. This suggests that there is actually a continuum of postural responses formed by the addition of hip torque to the ankle strategy, rather than two distinct strategies.

Feet-in-place strategies for responding to medio-lateral perturbation primarily involve the hip abductors and adductors, due to the limited capacity at the ankle and knee for motion and torque generation in the frontal plane. Although one might expect responses to perturbations in “off axis” or “diagonal” directions to involve a weighted combination of the medio-lateral hip strategy and the antero-posterior ankle strategy, it appears that this construct is inadequate to explain the complex muscle responses that are evoked by multi-directional perturbations. Rather, there appears to be a continuum of strategies that are modifiable in a task-dependent manner [9]. Thus, for example, there may be co-contraction of agonist and antagonist ankle muscles

(which serves to stiffen the ankle joint) and latencies for some muscles may differ according to the perturbation direction.

Although the feet in place strategies described above primarily involve activation of the lower limb and axial (trunk and neck) musculature, postural reactions involving the upper limbs often occur in parallel. In fact, activation of the arm muscles can occur as rapidly as the earliest activation at the ankle (80 ms after perturbation onset). The functional role of these arm-reaction strategies appears to vary, depending on task conditions. In situations where the hand is in contact with a supporting object or surface at time of perturbation onset, the arm reaction can rapidly generate stabilizing “environment reaction” forces at the hand. In situations where the arms are free to move, the arm movements may serve to augment the stabilization achieved by the lower limb reactions. For example, raising the arms can help to stabilize the body by acting as a counterweight, by inducing inertial joint torques at the shoulder (due to the acceleration and/or deceleration of the arm segments) or by increasing the rotational inertia of the body. In some situations, it appears that the raising of the arms may also serve a protective function, to absorb energy and reduce the risk of injury in the event that a fall does occur. It is also possible that the arm activation is related to an aborted [reach-to-grasp](#) [change-in-support strategy](#) (see below).

Change-in-Support Strategies

In change-in-support reactions, the BOS is altered via rapid stepping or reaching movements of the limbs. Increase in the BOS allows: (i) a larger range of perturbation-induced COM motion to be tolerated without loss of equilibrium, (ii) more time for this COM motion to be decelerated (via “environment reaction” forces generated at the foot and/or hand) and (iii) larger decelerating “environment reaction” forces to be generated (Fig. 2). Reach to grasp reactions provide a further biomechanical advantage in that they allow the body to be anchored with respect to the grasped object, provided that a sufficiently strong grip can be maintained. Change-in-support reactions can provide a much larger degree of stabilization, in comparison to fixed support reactions and are the only recourse in responding to large perturbations [1,3].

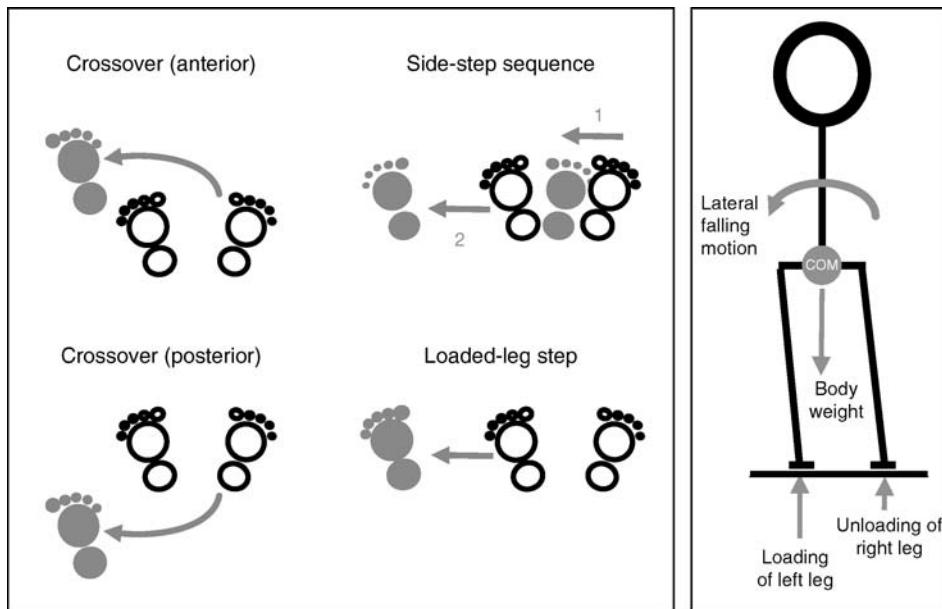
The neural control of change-in-support (compensatory) and volitional limb movements appear to differ in some fundamental ways. First, the compensatory postural movements are much more rapid. A compensatory stepping movement is typically completed in about 500 ms, approximately half the time required to step as fast as possible in reaction to a visual cue. Similarly, compensatory reaching reactions are more rapid than volitional arm movements. For example, compensatory arm activation typically begins at a

latency of 80 to 140 ms after perturbation onset, whereas the most rapid latency for volitional arm activation (single-choice reaction-time task) is about 150–200 ms (and is slower when the task involves multiple choices).

Another fundamental distinction between compensatory stepping and volitional stepping pertains to the presence or absence of an “anticipatory postural adjustment” (APA), prior to the lifting of the swing leg. Volitional movements that involve stepping or raising a leg are invariably preceded by an APA which acts to propel the COM toward the stance limb and thereby serves to reduce the tendency of the COM to fall laterally toward the unsupported side during the subsequent foot movement. The APA is typically either absent or severely truncated during compensatory stepping reactions. This allows more rapid step execution; however, the consequence is that the lateral COM motion arising during the swing phase must be arrested after the swing foot lands. A large APA does occur when task demands require a prolonged swing phase (e.g., when the compensatory step must clear an obstacle). Presumably, the APA is required in such situations because the COM has much greater opportunity to fall laterally.

Whereas antero-posterior perturbations typically (in healthy young adults) evoke a single step that is predominantly directed forward or backward, perturbations in other directions evoke a wider variety of stepping patterns. If the perturbation includes a medio-lateral component, then the perturbation induced COM motion will cause an increase in loading of one leg and a decrease in loading of the contralateral leg. Typically, when the perturbation is unpredictable, the unloaded leg is used to execute the stepping reaction. This has the advantage of allowing a more rapid foot lift, as less time is required to complete the unloading of the swing foot; however, the consequence is that a more complex stepping movement is required. This may involve a crossover step, in which the swing foot is moved across the body (either in front of or behind the stance leg). Alternatively, the unloaded leg may be used to execute a small initial medial step, which is then followed by a large lateral step with the contralateral leg (a “side-step sequence”). See Fig. 3.

The direction of perturbation-evoked reach-to-grasp reactions is highly dependent on both the direction of the perturbation and the location of potential handholds that can be grasped or touched for support. Remarkably, even the earliest portion of the arm trajectory (at a latency as early as 80 ms) is directed toward the nearest available handhold. Such a rapid response does not permit visual scanning of the environment; hence, it appears that the initial arm trajectory must either involve peripheral vision or “remembered” visuospatial information. In order to use “remembered” information,



Postural Strategies. Figure 3 ▶ **Stepping strategies** evoked when the postural perturbation includes a lateral component. The footprint drawings illustrate responses evoked by a perturbation that induces leftward falling motion of the center of mass (COM). The *unshaded* footprints indicate the starting position at time of perturbation onset, and the *shaded* footprints indicate the landing position of each step. The *stick figure* illustrates how the initial COM motion induced by this perturbation creates increased loading of the left leg. As a consequence of this loading, the stepping responses are most commonly initiated with the unloaded (right) leg, and involve either a crossover movement or a side step sequence (a small medial step followed by a large lateral step). Reactions where the initial step is taken with the loaded foot have been observed to occur very rarely in some studies, but more commonly in others. The “loaded leg” steps seem more likely to occur when the individual can preplan to step with a specific leg (e.g., if the direction of the perturbation is known in advance).

the CNS would need to maintain and automatically update an egocentric spatial map of the immediate surroundings as the person moves about in daily life. This would then allow the hand to be directed very rapidly toward the nearest available handhold, if and when sudden unexpected loss of balance occurs. A similar control mechanism would allow rapid perturbation-evoked stepping reactions to be directed appropriately, so as to avoid obstacles and accommodate other constraints on foot movement.

Although the neural pathways involved in the control of change-in-support reactions are not well established, it seems likely that the planning of the limb trajectory makes use of the same neural pathways as those thought to be involved in planning volitional limb movements, i.e., spinal pattern generators in the case of stepping reactions and cortical pathways in the case of reaching reactions. The very rapid initiation and scaling of the trajectory could then be triggered by subcortical pathways similar to those thought to be involved in triggering the early fixed-support postural reactions.

Strategy Selection

A traditional view has been that change-in-support reactions are only used as a last resort when earlier

fixed-support reactions fail to keep the COM within the stability limits of the BOS. The basic idea is that the ankle strategy is used to respond to antero-posterior perturbation when the induced COM motion is small in relation to the BOS stability limits, the hip strategy comes into play when the COM motion is larger, and stepping and reaching emerge only when the COM motion exceeds the stability limits of the BOS. This may be true when individuals are instructed to try not to step or move the arms; however, this is clearly not the case when the person is allowed to respond naturally. It is now clear that compensatory stepping and reaching are commonly initiated very early, with the COM well within the stability limits and in fact often seem to be the preferred response. For example, individuals will almost always step and begin to move the arms when the perturbation is unexpected or novel (e.g., the very first trial in an experiment), even if the perturbation is relatively small.

It appears that initiation of reach-to-grasp reactions occurs in parallel with the earliest fixed-support reaction, as evidenced by the similarity in timing of the arm and ankle activation (latency of ~100 ms). Typically, the initiation of compensatory stepping is not quite as rapid; however, the onset of the stepping

reaction (i.e., active changes in leg loading) can occur as early as 130 ms after perturbation onset. Interestingly, the early fixed-support reaction is not eliminated, even when a rapid reach-to-grasp or stepping reaction is initiated. Presumably, the fixed-support reaction persists as an important safeguard against instability. Early initiation of the change-in-support response, regardless of perturbation magnitude, may also reflect the high priority given by the CNS to the task of safeguarding stability.

Ultimately, strategy selection can be influenced by a number of factors, including (i) the features of the perturbation (timing, direction, magnitude, predictability), (ii) the “[central set](#)” of the individual (affect, arousal, attention, expectations, prior experience), (iii) ongoing activity (cognitive or motor) and (iv) environmental constraints (e.g., slippery surfaces that limit reaction-force generation, obstacles that constrain limb movement) [1,7,10].

Modulation of Strategies

Both fixed-support and change-in-support reactions are highly modifiable and adaptations to meet task demands can be learned rapidly (e.g., over the course of one to five experimental trials). The same factors that affect strategy selection listed above can also modulate many of the features of the reactions *per se*.

One of the features that is not highly modifiable is the timing of the early activation of the ankle muscles in the ankle strategy. This early activation typically persists, at a similar latency, even when the individual preplans to use a stepping reaction to recover balance, despite the fact that the ankle activation may interfere with the execution of the step. In keeping with the persistent and apparently automatic nature of this response, the early ankle activation is commonly referred to as the early “automatic postural response” (APR). Nonetheless, the APR is not a stereotyped response. The magnitude of the activation is scaled according to the direction and magnitude of the perturbation and is influenced by the predictability of the perturbation, the “central set” of the individual and the instructions given (e.g., whether or not to step). The functional task demands can also have a profound effect. For example, backward horizontal support surface movements evoke activation in the ankle plantarflexors, which serves to stabilize the body. When similar ankle rotation is evoked by toes-up tilt of the support-surface, the evoked plantarflexor activation acts to amplify the destabilization, but this non-functional response quickly habituates over the course of repeated trials in healthy individuals [10].

Change-in-support reactions exhibit an even greater degree of modifiability, in both magnitude and timing [1,3]. For example, initiation of stepping reactions can be delayed substantially by instructions to try not to step.

Conversely, stepping and reaching reactions can be initiated more quickly when the person is given prior instruction to step or reach in response to the perturbation. Furthermore, the limb movements are heavily dependent on environmental constraints (i.e., location of obstacles and potential handholds). There also appears to be capacity for online modulation. For example, the limb trajectory can be altered (to at least some degree) to deal with additional perturbations or changes in environmental constraints arising after initiation of the reaction and reactions that are initiated can be aborted prior to completion.

References

1. Maki BE, McIlroy WE (2003) Effects of aging on control of stability. In: Luxon L et al. (eds) A textbook of audiological medicine: clinical aspects of hearing and balance. Martin Dunitz, London, pp 671–690
2. Pai YC, Patton J (1997) Center of mass velocity-position predictions for balance control. *J Biomech* 30:347–354
3. Maki BE, McIlroy WE (1997) The role of limb movements in maintaining upright stance: the “change-in-support” strategy. *Phys Ther* 77:488–507
4. Allum J, Carpenter MG, Honegger F (2003) Directional aspects of balance control in man. *IEEE Eng Med Biol Mag* 22:37–47
5. Dietz V (1992) Human neuronal control of automatic functional movements: Interaction between central programs and afferent input. *Physiol Rev* 72:33–69
6. Maki BE, McIlroy WE (2007) Cognitive demands and cortical control of human balance-recovery reactions. *Journal of Neural Transmission* 114:1279–1296
7. Nashner LM, McCollum G (1985) The organization of human postural movements: a formal basis and experimental synthesis. *Behav Brain Sci* 8:135–172
8. Runge CF, Shupert CL, Horak FB, Zajac FE (1999) Ankle and hip postural strategies defined by joint torques. *Gait Posture* 10:161–170
9. Henry SM, Fung J, Horak FB (1998) EMG responses to maintain stance during multidirectional surface translations. *J Neurophysiol* 80:1939–1950
10. Horak FB (1995) Adaptation of automatic postural responses. In: Bloedel J et al. (eds) Acquisition of motor behavior in vertebrates. MIT, Cambridge MA

Postural Sway

Definition

In stance, a process of continuous, small corrections of the upright body position takes place to oppose the destabilizing effect of gravity. This creates a pattern known as spontaneous sway, or postural sway.

►Stabilometry

Postural Synergies

LENA H. TING

Laboratory for Neuroengineering, The W. H. Coulter
Department of Biomedical Engineering, Emory
University and Georgia Institute of Technology,
Atlanta, GA, USA

Synonyms

Muscle synergies; functional muscle synergies; motor primitives; M-modes

Definition

A ►**postural synergy** is a preferred pattern of muscle co-activation that is used by the nervous system to maintain standing balance. Each postural synergy specifies a pattern of muscle activation across many muscles. Through flexible combinations of postural synergies, a repertoire of postural behaviors is produced. By eliminating the need to control each muscle independently, postural synergies are thought to simplify the neural control task of selecting and coordinating multiple muscles across the body. A postural strategy defines the overall goals involved in the maintenance of balance; these can vary depending on the particular postural task, the context in which the task is performed and the postural configuration. Postural synergies define the muscle activation patterns that are used by the nervous system to implement various postural strategies.

Description of the Theory

Introduction

The theory of postural synergies address the basic question of whether the nervous system activates each muscle independently when it performs a task or whether the multiple muscles are activated together, thus reducing the total number of neural command signals necessary. Currently, postural synergies are thought to represent neural “building blocks” for generating a wide range of postural behaviors. Each postural synergy specifies a pattern of muscle activation across many muscles and is purportedly controlled by one neural command signal. By combining muscle synergies in various proportions, a continuum of muscle activation patterns for postural control can be generated using just a few neural command signals.

The long-standing debate within the general motor control field over the concept of muscle synergies is exemplified by the specific debate over the existence of postural synergies. Nashner first described “fixed” postural synergies in subjects standing on a moving perturbation platform [1]. Distinct patterns of muscle activation across the ankle, knee, hip and trunk were

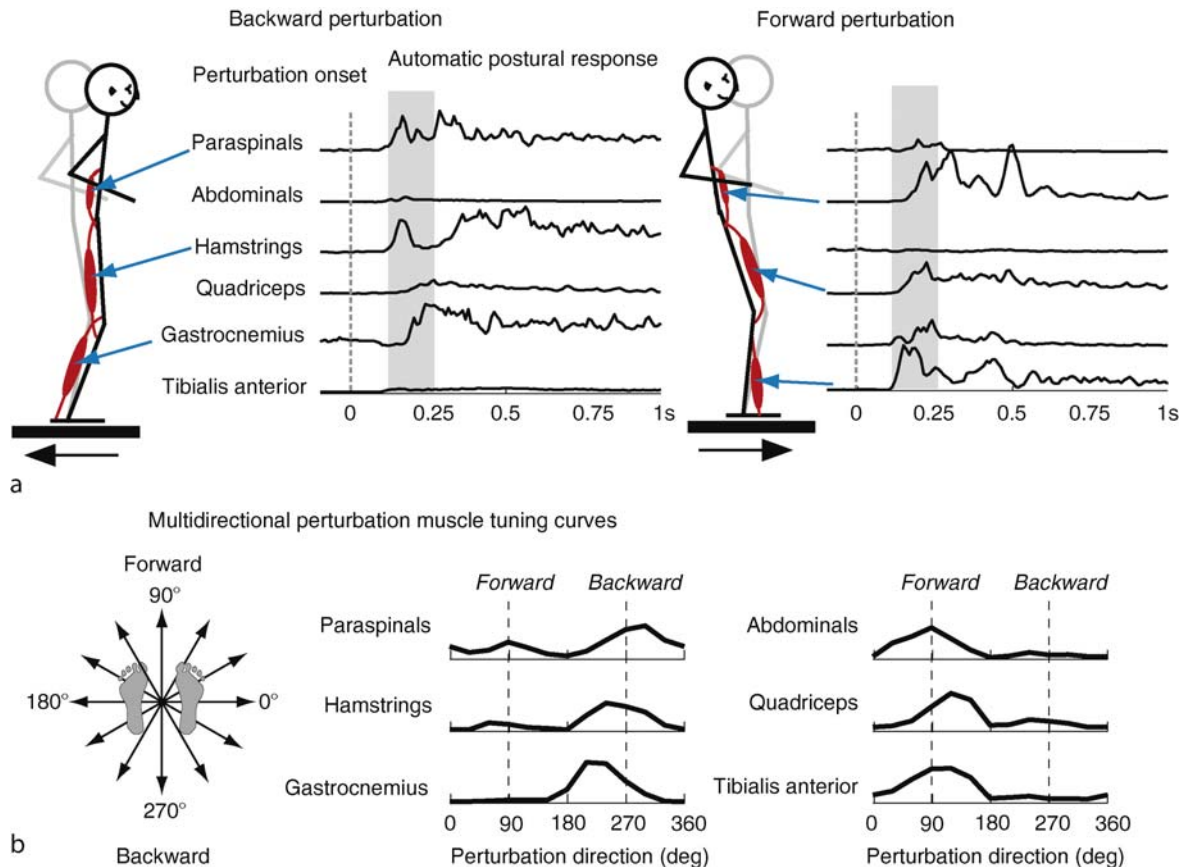
reliably observed when the platform was moved either forwards or backwards (Fig. 1a) and were thought to represent two different postural synergies [2]. Originally, it was thought that postural synergies were activated in a mutually exclusive fashion and that each muscle was activated by only one postural synergy (Fig. 2a).

These conclusions were challenged by later studies that showed flexibility in patterns of muscle activation in response to a backward perturbation. Depending on the perturbation amplitude and prior experience of the subject, two types of responses were observed, the “ankle strategy” and the “hip strategy,” so named for the major joint motions involved. Each strategy elicits a very different pattern of muscle activation, demonstrating that postural synergies to a particular direction of perturbation are not fixed. Moreover, when perturbations were given in many directions in the horizontal plane, even more complex patterns of muscle activation emerged in both humans and cats [2]. Each different perturbation direction elicited a unique pattern of muscle activation (Fig. 1b), suggesting that muscles must be controlled independently to perform multidirectional balance control. It was for this reason that the notion of muscle synergies was then rejected as being too constraining and inflexible for the production of natural movements [3].

Recently, new computational techniques have helped to demonstrate that a motor control architecture based on muscle synergies can both simplify neural control as well as provide flexibility in motor output. In the new framework, more than one muscle synergy can be activated during a postural response and each muscle can also be activated by more than one synergy. By varying the magnitude of the neural command signals to just a few muscle synergies, many different muscle activation patterns can be generated (Fig. 2b), including the responses to multidirectional postural responses describe above [4]. The neural substrates of muscle synergies for postural control remain unknown. Where muscle synergies are encoded within the neural control hierarchy is a complex topic and may also be task dependent. It is hypothesized that postural synergies are formed in the brainstem, based on observations of postural control following neural impairment.

Degrees of Freedom Problem

To maintain standing balance, the nervous system must confront the classic “degrees of freedom” problem posed by Nikolai Bernstein [5], where many different solutions are available due to the large number of elements or degrees of freedom involved. In postural control, a large number of muscles and joints across the limbs, trunk and neck must be coordinated to maintain the body’s ►**center of mass (CoM)** over the base of support, typically formed by the feet. The large

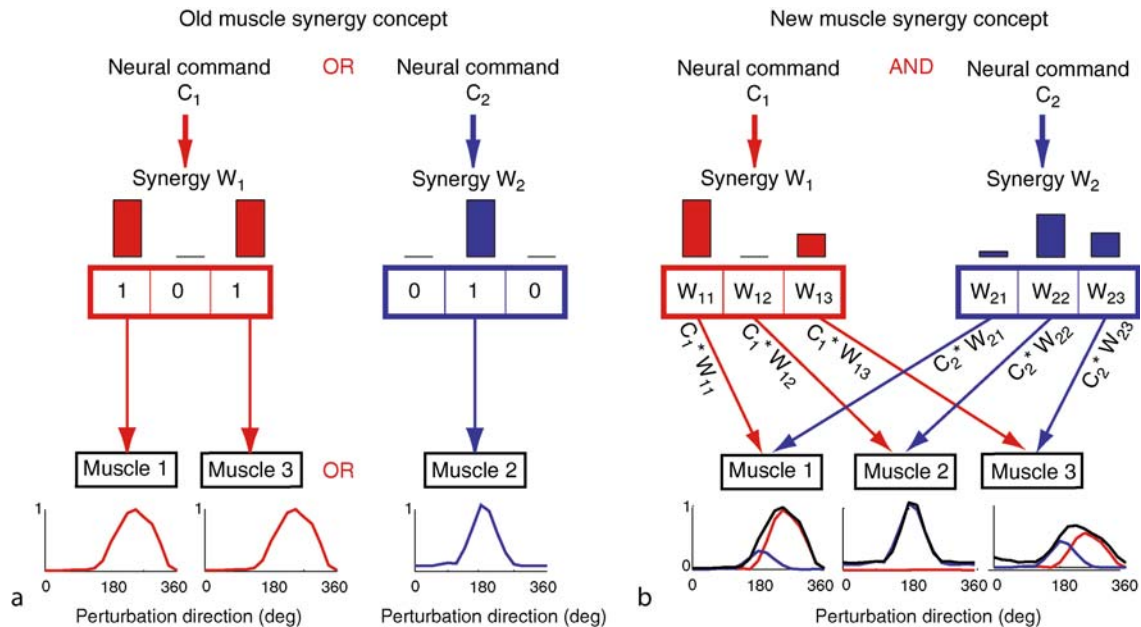


Postural Synergies. Figure 1 Muscle activity evoked following perturbations to the support-surface. (a) Backward perturbations elicit activity in muscles on the posterior side of the body. (b) Forward perturbations elicit activity in muscles on the anterior side of the body. The gray area represents the initial muscular response to perturbation, called the automatic postural response (APR). (c) The magnitude of the response during the APR varies as a function of direction and can be plotted as a tuning curve. Each muscle has a unique tuning curve, suggesting that each muscle is activated by a separate neural command signal.

number of degrees of freedom afforded by the multiple joints and muscles in the body thus allow for many solutions that can accomplish the task goals equally well. This multiplicity or redundancy of solutions allows flexibility in performing the postural task; it also poses the problem that the nervous system must choose from a large set of possible solutions. In contrast, if the body were a simple rigid stick balanced on one end, then the angle of the stick in space would completely determine the location of the center of mass with respect to the base of support. Moreover, if only one muscle is available, there is no ambiguity as to how to activate the muscle in order to move the center of mass. Thus, the “degrees of freedom problem” occurs only when overall task requirements are not sufficient to specify multiple output variables controlled by the nervous system.

Bernstein proposed the existence of synergies as a neural strategy for simplifying the control of multiple degrees of freedom by coupling or grouping output

variables [5]. This scheme was based on experimental observations that many joint angles appear to be controlled together rather than independently during motor tasks. For example, during locomotor tasks such as running, the hip, knee and ankle joints all flex and extend at the same time, suggesting that they are not controlled independently. However, such observations only identify correlations between the joint motions. A variety of muscle activation patterns can produce similar joint movements. Therefore, joint angle changes do not necessarily have a direct relationship to neural command signals activating muscles. Since muscle activation is directly caused by motoneuron firing, correlations between muscle activation patterns can be more plausibly derived from a single neural command that is distributed across the various motoneuron pools. Thus, muscle synergies may represent a mechanism by which the nervous system can achieve repeatable multijoint coordination.



Postural Synergies. Figure 2 Illustrations of two different muscle synergy concepts. (a) In the original muscle synergy concept, only one muscle synergy was elicited at a time, and muscles could only be activated by one synergy. Therefore, all muscles activated by the same synergy would have the same directional tuning curve, determined by the neural command c that activated it. (b) In the new concept, more than one synergy can be activated at a time. Further, muscles can participate in multiple synergies, and have different weightings in each synergy. Therefore, each muscle's tuning curve is a weighted average of the two tuning curves of each muscle synergy.

Computational Methods for Identifying Postural Synergies

Recent computational techniques have redefined the working hypothesis of how muscle synergies can allow for flexible motor coordination while also simplifying the degrees of freedom problem. In this new formulation, a single synergy specifies a fixed muscle activation pattern that is modulated by a single neural command signal, but multiple muscle synergies can be activated at one time [4,6,7]. Mathematically, each muscle activation pattern is thus composed of a linear combination of a few (n) muscle synergies $\mathbf{W}_i$, each activated by one neural command c_i . The net muscle activation pattern vector $\mathbf{M}$ is therefore hypothesized to take the form:

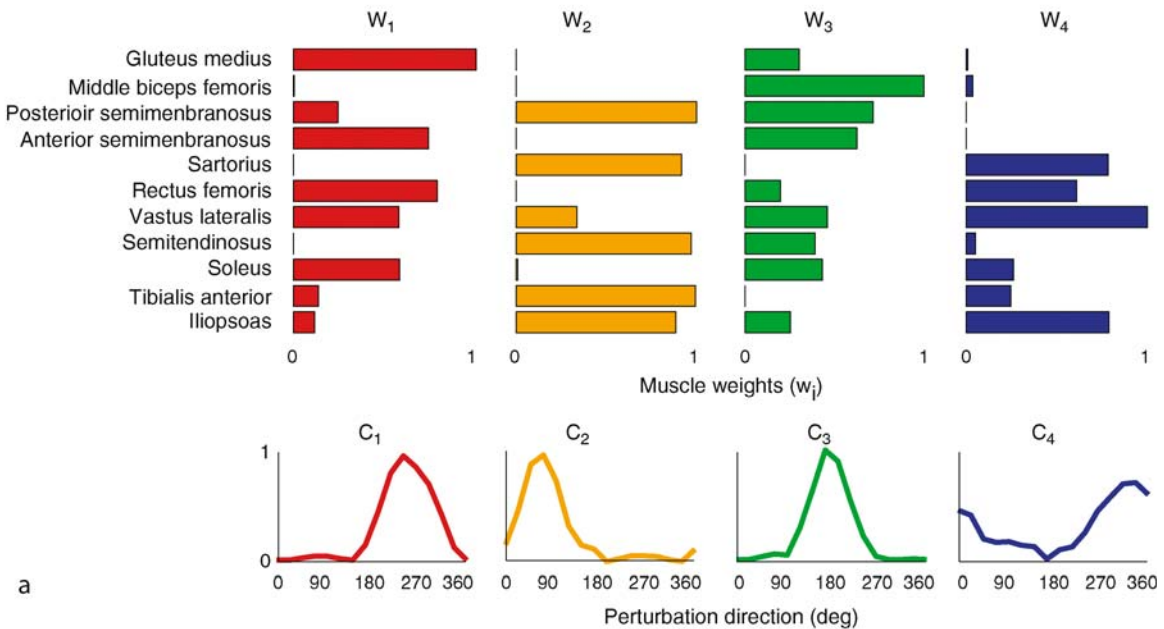
$$\mathbf{M} = c_1 \mathbf{W}_1 + c_2 \mathbf{W}_2 + \dots + c_n \mathbf{W}_n$$

$\mathbf{M}$ is a vector where each element is the resulting level of activation in each muscle (Fig. 3a). $\mathbf{W}_i$ is a vector that specifies the pattern of muscle activity defined by that muscle synergy. Each element of $\mathbf{W}_i$ takes a value between 0 and 1, representing the relative contribution of each muscle to that muscle synergy. Each muscle synergy is then activated by a single, scalar neural command signal c_i , which determines the relative contribution of the muscle synergy $\mathbf{W}_i$ to the overall muscle activation pattern, $\mathbf{M}$.

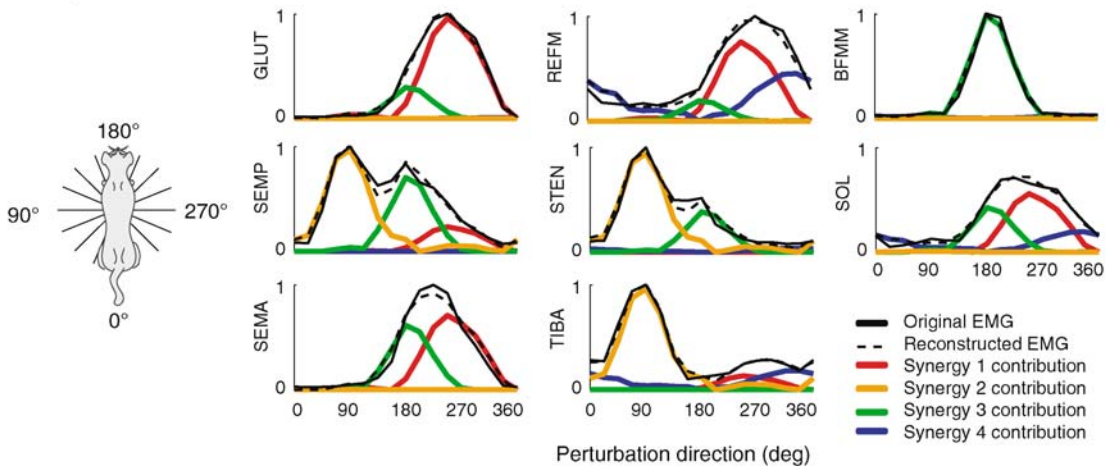
The above formulation allows for flexible “mixing” of a set of muscle synergies to produce the final output muscle activation pattern. Therefore, if two muscle synergies are present, rather than defining just two output muscle activation patterns, as in previous definitions (Fig. 2a), an entire continuum of output muscle activation patterns can be generated by varying the commands c_1 and c_2 . Within this continuum, individual muscle activations are not strictly correlated to each other because most muscles belong to more than one muscle synergy and are thus activated independently by two different neural commands (Fig. 2b).

Linear decomposition techniques can be used to identify muscle synergies from experimentally measured muscle activation patterns. Because the number of muscle synergies is smaller than the number of muscles for any given task, the spectrum of muscle activation patterns that can be generated using muscle synergies is more limited than the case where muscles are controlled independently. However over the entire behavioral repertoire the number of muscle synergies could exceed the number of muscles. This dimensional reduction, which simplifies the degrees of freedom problem, can be identified using several mathematical analysis techniques such as principal components analysis (PCA), independent components analysis (ICA) and factor analysis (FA) [6]. Another such technique, non-negative matrix factorization (NMF),

Muscle synergies (W) and neural commands (C)



Muscle tuning curve reconstruction



Postural Synergies. Figure 3 Muscle synergies and neural commands used to generate muscle tuning curves during postural responses in cats. (a) Each muscle can participate in each muscle synergy with a different weight, indicated by the bars. (b) Neural commands to each muscle synergy can also be illustrated as tuning curves. Each muscle synergy therefore has preferred direction of activation. (c) EMG tuning curves can be reconstructed using muscle synergies. Each muscle's tuning curve is found by summing the product of each tuning curve, c_i and the weighting of each muscle within the synergy W_i . All muscle tuning curves are thus constrained to be weighted averages of the synergy tuning curves. Therefore, the muscle tuning curves have more varied and complex shapes than the synergy tuning curves.

allows complex data sets to be more successfully partitioned into meaningful parts [4,6,8]. NMF is particularly useful for data that are inherently positive valued, such as neural spike trains or muscle activations. The extracted elements are based on the components forming the data set rather than on more holistic features. For example, when applied to images of faces, a non-negative extraction routine generates vectors representing

noses, ears and eyes, whereas PCA generates components that all tend to look roughly like an entire face [8].

Muscle Synergies in Postural Control

During postural responses to perturbations in different directions, multiple muscles across the body are activated and for each different direction of the perturbation, a different pattern of muscle activation is

elicited (Fig. 1b). In both humans and in cats, a stereotyped, directionally specific pattern of muscle activity called ▶automatic postural response (APR) is evoked after perturbations to the support surface. The muscle activation occurs after the platform motion begins, but before the center of mass moves appreciably, with a latency of around 50 ms in the cat and 100 ms in humans. In both cases, this latency is about twice the ▶stretch reflex latency for distal muscles and evokes a much larger response than the stretch reflex [2]. Each muscle's activation level can be expressed in terms of a muscle tuning curve, which shows the variation of the muscle activation with perturbation direction (Fig. 1b – human, Fig. 3b – cat). Thus, for some directions, a muscle may have high activation and for others it may not be active at all. These muscle tuning curves define the complex patterns of muscle activation evoked across many perturbation directions [2,4,9].

Although each direction of perturbation evokes a slightly different pattern of muscle activation over all muscles, these variations can be explained by a combination of just a few muscle synergies in the cat [4]. Over 95% of the variability in as many as fourteen muscle tuning curves can be explained by combining just four muscle synergies (Fig. 3b). Instead of activating each muscle independently for each perturbation direction, only four neural commands, each activating a synergy W_i , need to be specified with amplitude c_i for any perturbation direction. The net muscle activation pattern is thus found by adding up the contributions of each muscle synergy to each muscle's activation level.

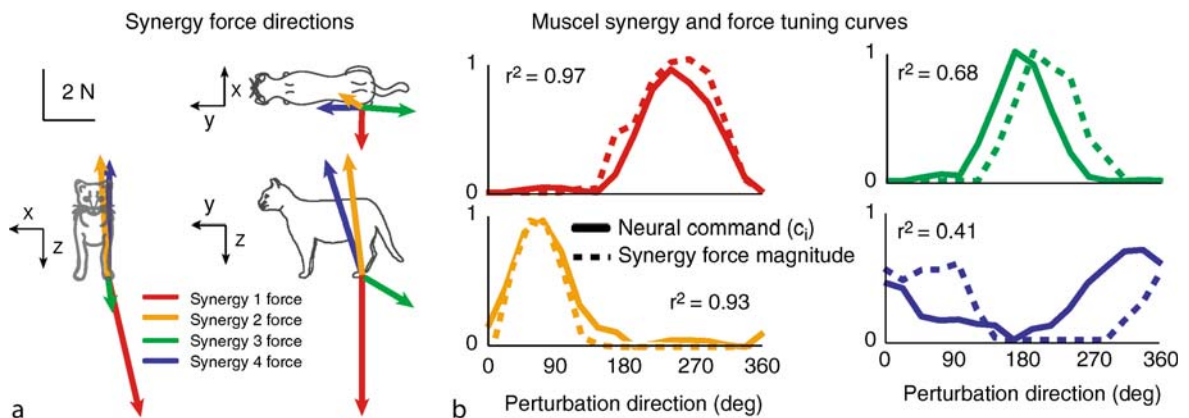
Muscle synergies may coordinate the limb to produce a specific biomechanical function for stabilizing the body. In the cat, it has been suggested that each muscle synergy allows the leg to produce a force in a particular

direction in order to stabilize the leg (Fig. 4a). Variations in the components of active force generated by each leg are correlated to the variations in the neural commands of each muscle synergy (Fig. 4b). Each muscle synergy can generate a specific direction of force; the forces are distributed so that upward, downward, anterior, posterior and lateral force direction can be produced. Thus, muscle synergies may be organized to produce specific task-level biomechanical functions [4].

Even for postural perturbations of the same direction, multiple muscle synergies may exist. In backward perturbations of the support surface in humans, two types of responses can be elicited. One is called the “ankle strategy” where the body remains upright and most of the motion occurs around the ankle joint. The other is called the “hip strategy,” where the trunk tilts forwards and the hip angle motion is most predominant. Each strategy can be defined by a specific pattern of joint torques. Because joint torques directly relate to the force generation of the musculature, this suggests that there are muscle synergies underlying these two strategies. While these two strategies were initially thought to be mutually exclusive, they in fact represent two different postural synergies that can be combined to produce a whole continuum of intermediate responses [2,11]. Therefore, rather than having a simple repertoire of just two response patterns, the flexible combination of these postural synergies allows the APR to be tuned and varied with perturbation amplitude, prior experience and anticipation.

Encoding of Muscle Synergies in the CNS

If muscle synergies reflect neural control mechanisms, then what are the neural substrates that generate muscle synergies? It is now understood that postural synergies



Postural Synergies. Figure 4 Forces produced during the automatic postural response correlate with muscle synergy activations. (a) Forces produced during postural responses can be decomposed into four force vectors. (b) During postural response, the magnitude of each force vector required to reproduce the total force varies as a function of direction and can be illustrated as a tuning curve. The tuning curves of force magnitude are highly correlated with the tuning curves of the neural commands c_i activated the muscle synergies. Thus, each force vector may represent the functional output of the muscle synergy.

cannot be explained just by reflexes acting in response to muscle stretch. In both humans and cats, it has been shown that perturbations that stretch the muscles differently can activate the same muscle synergies. For example, Nashner originally demonstrated that for a backward translation of the support surface, the calf muscle is stretched as the subject falls forward and that the same muscle is subsequently activated to maintain balance, consistent with a stretch reflex. In contrast, if a toes up rotation of the support surface is given, the calf muscle is stretched but the subject falls backwards, so that the antagonist muscle is activated to restore balance, in direct opposition to the stretch reflex [1]. This same principle has been demonstrated in multidirectional perturbations in both cats and humans [9]. Moreover, the loss of a single sensory modality, such as proprioceptive, vestibular or visual loss, does not appear to significantly affect muscle activation patterns, only their activation levels. Therefore muscle synergies are not a direct response to local sensory input, but appear to be related to more global variables, such as the direction of CoM displacement caused by the perturbation, that require multisensory integration [2,9].

How postural synergies are encoded in the nervous system is not known. For locomotor tasks, the encoding of muscle synergies appear to be located within the neural circuitry of the spinal cord [7], as animals can produce locomotor activity from a spinal cord that is isolated from the brain following spinal cord transection. These same animals can support their own weight while standing, but direction specific responses to postural perturbations are lost. This suggests that postural synergies are generated within the spinal cord [10]. It is known that the brainstem is essential to the maintenance of postural orientation and equilibrium and it is possible that neural mechanisms producing postural synergies reside there. Moreover, postural synergies appear intact in patients with postural impairments due to lesions in higher brain centers. For example, Parkinson's disease is characterized by pathology of the basal ganglia, which project to brainstem areas that are important for postural control. Individuals with Parkinson's disease have the ability to generate postural synergies that are similar to control subjects, but have difficulty changing the muscle synergy that is activated when perturbation conditions change. Similarly, in individuals with cerebellar dysfunction, postural synergies are similar to control subjects, but their activation levels do not decrease with repeated perturbations as in control subjects. Therefore, the muscle synergy structure appears intact, but the ability to correctly activate the neural commands to those muscle synergies is compromised, which impairs the postural stability in these individuals [2]. The theory of postural synergies therefore contributes to our understanding of the role of various nervous system structures in postural

control and can guide experimental investigations that may further the validity of the theory.

► Postural Strategies

References

1. Nashner LM (1977) Fixed patterns of rapid postural responses among leg muscles during stance. *Exp Brain Res* 30(1):13–24
2. Horak FB, Macpherson JM (1996) Postural orientation and equilibrium. In: *Handbook of physiology*, Section 12. American Physiological Society, New York, pp 255–292
3. Macpherson JM (1991) How flexible are muscle synergies? In: Humphrey DR, Freund H-J (eds) *Motor control: concepts and issues*. Wiley, New York, pp 33–47
4. Ting LH, Macpherson JM (2005) A limited set of muscle synergies for force control during a postural task. *J Neurophysiol* 93(1):609–613
5. Bernstein N (1967) *The coordination and regulation of movements*. Pergamon, New York
6. Tresch MC, Cheung VC, d'Avella A (2006) Matrix factorization algorithms for the identification of muscle synergies: evaluation on simulated and experimental data sets. *J Neurophysiol* 95:2199–2212
7. Flash T, Hochner B (2005) Motor primitives in vertebrates and invertebrates. *Curr Opin Neurobiol* 15(6):660–666
8. Lee DD, Seung HS (1999) Learning the parts of objects by non-negative matrix factorization. *Nature* 401(6755):788–791
9. Ting LH, Macpherson JM (2004) Ratio of shear to load ground-reaction force may underlie the directional tuning of the automatic postural response to rotation and translation. *J Neurophysiol* 92(2):808–823
10. Macpherson JM, Fung J (1999) Weight support and balance during perturbed stance in the chronic spinal cat. *J Neurophysiol* 82(6):3066–3081
11. Torres-Oviedo G, Ting L (2007) Muscle synergies characterizing Human postural responses. *J Neurophysiol* 98:2144–2156

Postural Tone

Definition

Background tension developed by the antigravity muscles. It represents a prerequisite for the maintenance of posture. The postural tone is regulated by intrinsic properties of spinal motoneurons, by the tonic activity of the corresponding muscle spindle afferents and by signals arising from brainstem systems projecting to the spinal cord, including the vestibular nuclei and the reticular formation.

► Postural Synergies

► Vestibulo-Spinal Reflexes

Postural Tremors

Definition

These tremors occur while trying to keep a body part in a constant position, such as an arm in outstretched posture.

Posture

Definition

A particular position assumed by the body.

Posture – Sensory Integration

ROBERT J. PETERKA

Neurological Sciences Institute, Oregon Health & Science University, Portland, OR, USA

Synonyms

Sensor fusion

Definition

Sensory integration, as it pertains to posture, refers to the process by which ►kinematic (orientation and motion) and ►kinetic (force related) information from multiple sensory sources is combined in the nervous system for the purpose of generating motor action to compensate for the destabilizing effect of gravity and to resist external perturbations.

Description of the Theory

The Task of Sensory Integration

Sensory information that is relevant to postural control is available from various sensory systems. These include the visual system, vestibular system, various aspects of somatosensation (proprioception signaling muscle stretch and joint angle, tendon force sensors, pressure sensors in the feet and other parts of the body signaling contact with the ground or the environment and tactile sensors in the skin around the joints) and the auditory system. Within each system, different subsystems encode physical variables related to different aspect of motion and orientation and related to forces applied to the body and within the body. Furthermore,

within each subsystem, the individual sensory receptors typically have a variety of static and dynamic response characteristics. The monumental task of the sensory integration process is to somehow combine this information and make it available to the motor control system so that the organism generates coordinated motor actions that maintain stability, respond appropriately to external perturbations and permit the expression of voluntary actions.

Benefits of Sensory Integration

In many situations the orientation cues provided by different sensory systems are redundant. Consider the simplest possible case where the legs, trunk and head of a human subject move together as a single mechanical unit with body sway consisting of a rotation about the ankle joints. In this case, during stance on a level surface while viewing an earth fixed visual scene, body sway relative to earth vertical is accurately sensed by the visual system, which signals body motion relative to the visual scene, by the vestibular system, which signals body motion in space and by proprioceptors, which signal ankle joint angle. However, there is variability and therefore uncertainty associated with orientation estimates derived from each of these sensory systems. In this common situation with redundant sensory information, an orientation estimate with reduced overall variability can be obtained by appropriately combining the redundant sensory information.

What is the appropriate way to combine redundant sensory information? Previous theoretical and experimental work suggests that the nervous system may employ the principle of maximum likelihood estimation to combine sensory inputs [1]. For the case of two sensory sources, S_a and S_b , the combined maximum likelihood estimate, $\hat{S}$, is given by a weighted combination of the individual sensory estimates

$$\hat{S} = w_a \cdot S_a + w_b \cdot S_b$$

where the sensory weights w_a and w_b are equal to

$$w_a = \frac{\sigma_b^2}{\sigma_a^2 + \sigma_b^2}, \quad w_b = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_b^2}$$

with σ_a^2 being the variance of S_a , and σ_b^2 the variance of S_b . In words, the sensory source with the smaller variance will have the larger weight and will make a larger contribution to the overall sensory estimate $\hat{S}$. Although an intuitive method for combining sensory information might be to ignore information from the more variable source, the maximum likelihood principle shows that the best (lowest variance) estimate is obtained by a weighted combination, even though one source may be considerably less reliable (i.e., large noise or variance) than the other source.

It is not currently known if the maximum likelihood principle strictly applies to sensory integration for postural control. However, it is known that a sensory weighting mechanism can account for experimental results in humans where body sway was provoked by tilts of the support surface or visual surround [2].

Constraints on Sensory Integration

Because postural control involves motor action as well as sensory integration, there are additional constraints on the sensory integration process as well as opportunities for the sensory integration process to facilitate postural control. Consider a simplified representation (Fig. 1) of a ►postural control system where orientation information is provided by proprioceptors and ►graviceptors.

Graviceptors yield the sensory signal S_{bs} that encodes the physical variable, BS (i.e., body in space angular orientation). Proprioceptors yield the sensory signal S_{bf} that encodes the physical variable BF (i.e., body orientation relative to the feet). It can be hypothesized that a weighted combination of these sensory sources contributes to an overall estimate of orientation, $\hat{S}$, and this overall estimate is compared to an internal reference orientation, S_{ref} , that represents the desired body orientation. Without loss of generality, it can be assumed that $S_{ref} = 0$ to symbolize the desired goal of remaining in an upright orientation. The difference between the orientation estimate and the reference orientation gives

a sensory “error” signal, e . This process is represented by the equation

$$e = \hat{S} - S_{ref} = w_p \cdot S_{bf} + w_g \cdot S_{bs} \text{ (for } S_{ref} = 0 \text{)}$$

where w_p is the proprioceptive weighting factor and w_g the graviceptive weighting factor. Then, through a sensory to motor transformation, a corrective torque, T_c , is generated as a function of e , $T_c = f(e)$, and T_c is applied to the body to control body orientation in space.

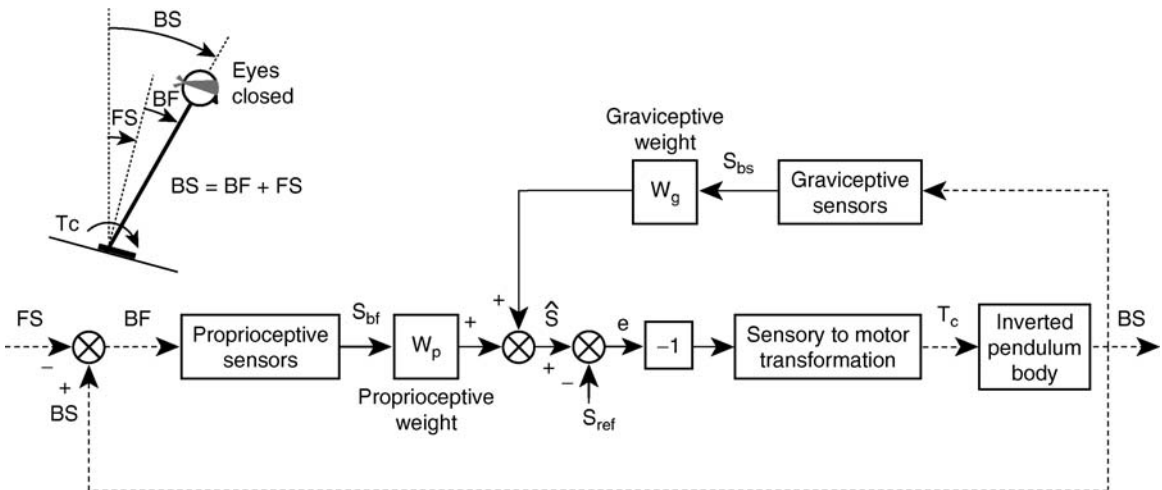
The net result of the process of sensory encoding, sensory integration and sensory to motor transformation is that T_c is generated as a function of a weighted combination of the physical variables BF and BS

$$T_c = f(w_p \cdot BF + w_g \cdot BS)$$

During stance on a level surface, the physical variables BF and BS are equal and the torque generated in relation to both proprioceptive and graviceptive cues facilitates maintenance of a stable vertical body orientation. However, on a tilting surface, BF is equal to $BS - FS$, where FS is the orientation of the feet in space (and equal to the tilted surface orientation assuming that the feet remain in contact with the surface). Therefore the above equation can be rewritten as

$$T_c = f(w_p \cdot (-FS) + (w_p + w_g) \cdot BS)$$

This equation shows that there are two components to T_c and these components have opposite signs. One



Posture – Sensory Integration. Figure 1 A block diagram representation of a sensory integration scheme for postural control based on a weighted combination of sensory orientation signals. In this example, proprioceptors are assumed to encode body orientation relative to the feet (BF) and graviceptors encode body in space orientation (BS). A weighted combination of these sensory signals is compared to an internal reference orientation (S_{ref}) and the resulting error, e , is used to generate a corrective torque, T_c , via a sensory to motor transformation process. The corrective torque acts on the body to change body orientation in space and relative to the feet. The block with -1 indicates a sign inversion such that a positive value of e produces a negative T_c that tends to drive the body back toward an upright orientation. The *dashed lines* connecting boxes indicate physical variables, and the *solid line* represents neural signals. The *inset stick figure* defines the positive direction of the physical variables.

component is related to *FS*. This component can be considered to be an undesirable disturbance torque that causes the body to align with the tilted surface and therefore would be destabilizing. The other component is related to *BS*. This component can be considered to be a desirable, stabilizing torque that causes the body to remain oriented with respect to earth vertical.

Now it is clear that an adjustment in the sensory weights can have an influence that goes beyond the consideration of optimal maximum likelihood estimation. Specifically, a reduction of w_p reduces the disturbance torque produced by surface tilt. A reduction in the disturbance torque would seem to be a desirable effect, except that a reduction in w_p also reduces the magnitude of the stabilizing torque related to *BS*. The magnitude of this stabilizing torque must be maintained above the level needed to counteract torque due to gravity. Furthermore, analysis of the postural control system in Fig. 1 indicates that the overall stabilizing torque level must be closely regulated in order to maintain stable, non-resonant behavior [3]. The dual task of reducing the destabilizing torque associated with surface tilt and maintaining adequate stabilizing torque can be accomplished by increasing w_g in equal proportion to the reduction in w_p [4]. This reciprocal adjustment of sensory weights is termed a **►sensory re-weighting** strategy and is also related to the concept of **►sensory substitution**. Therefore, a sensory integration mechanism that uses a weighted combination of sensory orientation sources can facilitate postural control by selecting weights to provide a low variance estimate of orientation in conditions where sensory systems provide redundant information and by adjusting weights to limit the effects of external disturbances while simultaneously maintaining stability.

The sensory integration mechanism shown in Fig. 1 is easily extended to include sensory information from vision [2] and other sensory systems by adding additional feedback loops, each with its own sensory weighting factor.

Combining Kinematic and Kinetic Information

The above discussion focused on combining information from kinematic sensors signaling body motion relative to the surface and relative to earth vertical. Integrating kinetic (force related) sensory information with kinematic information affords a further opportunity to enhance the capabilities of the postural control system. Fig. 2a shows a sensory integration scheme that includes a feedback path whereby a sensory signal encoding corrective torque contributes to the sensory error signal e .

Note that for the kinematic sensors, a forward (positive sign) body sway on a level surface produces a negative corrective torque that tends to restore body orientation to the upright position. That is, the

kinematic sensors are organized within the postural control system to provide **►negative feedback control**. However, a negative corrective torque sensed by the kinetic sensors produces an even larger negative torque. That is, the kinetic sensors are organized to provide **►positive feedback control**.

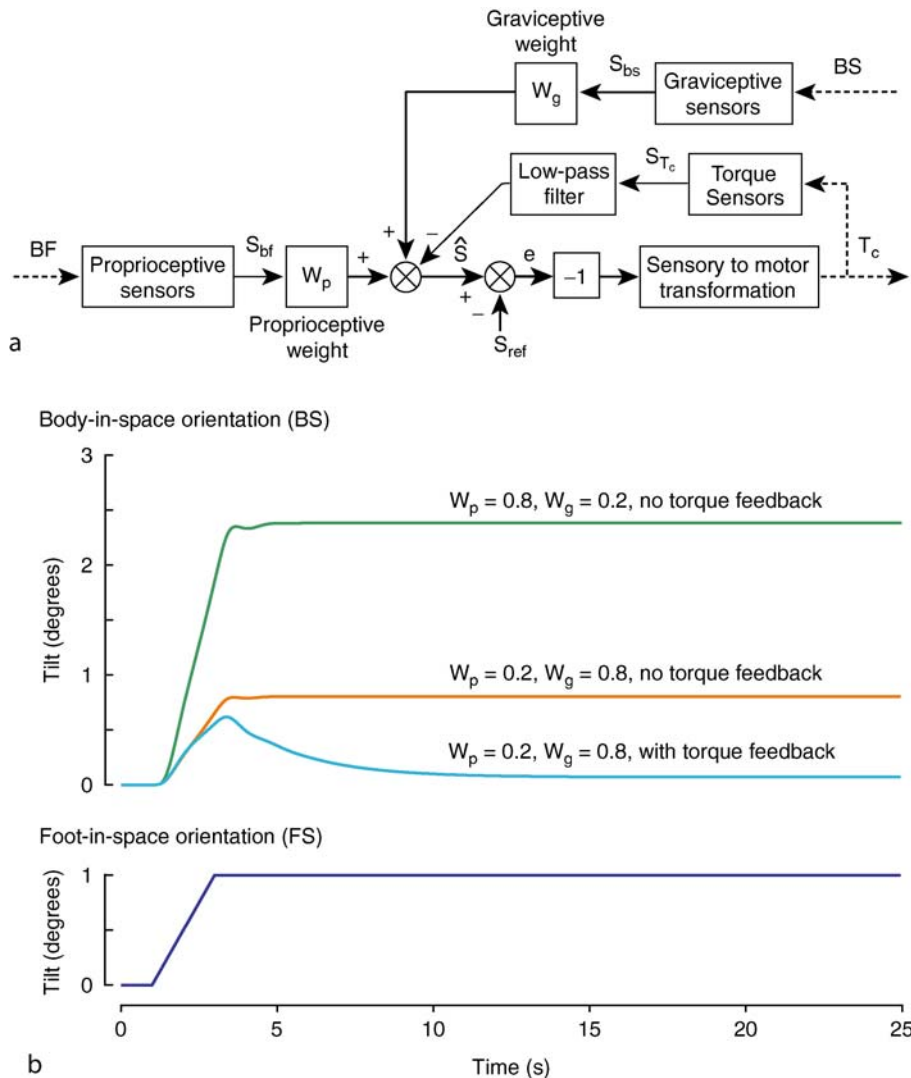
The benefit of integrating a kinetic contribution with kinematic sensory sources is illustrated in Fig. 2b. With only kinematic control, the Fig. 1 model predicts that a surface tilt of 1° produces a large body tilt of about 2.4° if the sensory integration relies primarily on proprioception ($w_p = 0.8$, $w_g = 0.2$). Body tilt is reduced to about 0.8° if a sensory re-weighting occurs that shifts toward increased reliance on **►graviception** ($w_p = 0.2$, $w_g = 0.8$). When kinetic sensory information is integrated with the kinematic information using the positive feedback mechanism shown in Fig. 2a, the surface tilt induces only a transient body tilt. Note that the time course of responses to surface tilt depends on the sensory integration mechanism, the properties of the sensory to motor transformation and body mechanics. For the results shown in Fig. 2b, the sensory to motor transformation generated T_c in proportion to e and to the rate of change of e , and included a time delay representing the combined delays attributable to sensory transduction, neural transmission, central processing and muscle activation. The torque feedback loop included a low pass filter, which implies that torque feedback mainly influences tonic or low frequency behavior of the postural control system [4].

Alternative Mechanisms for Sensory Integration

Although sensory integration can be modeled as a sensory weighting process, there are alternative representations that may correspond more closely to actual central nervous system processes. One idea is that the nervous system uses sensory information to reconstruct an internal representation of the external physical reality. As an example, Fig. 3 shows a sensory integration mechanism whereby proprioceptive and graviceptive sensory signals are used to reconstruct an internal representation of foot in space orientation.

Even though there are no direct sensors of foot in space orientation, the nervous system now has access to a derived representation of this important physical variable that encodes the surface orientation (assuming the feet are in contact with the surface). This internal representation of surface orientation provides an internal base upon which the nervous system can apply a hierarchical set of transformations that can be used to encode the orientation of various body segments relative to the surface [6].

Figure 3 also shows a scheme for combining the various internal representations of body orientation for the purpose of generating an overall error signal, e , which is the basis for generating the corrective torque

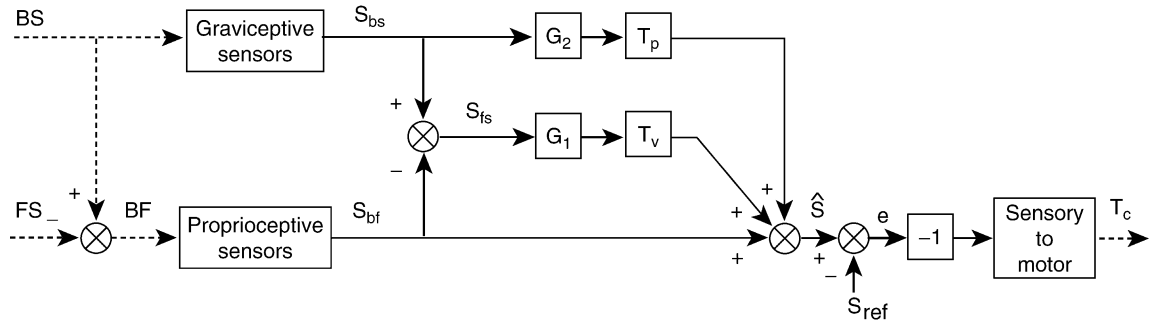


Posture – Sensory Integration. Figure 2 a Representation of a sensory integration scheme that includes a torque feedback contribution in addition to the weighted combination of proprioceptive and graviceptive cues shown in Fig. 1. The corrective torque, T_c , is assumed to be encoded, low pass filtered and then combined with other sensory signals via a summation with a sign opposite to those of the other sensory signals. Thus a positive value of T_c produces an even larger positive value of T_c , which facilitates the return of the body toward an upright position. b Examples of body sway responses evoked by a 1° tilt of the surface orientation (*lower blue trace*) for different sensory integration configurations. The predicted body sway is shown for different combinations of weighted sensory feedback both with and without torque feedback. See [4] for details regarding the postural control model and model parameters.

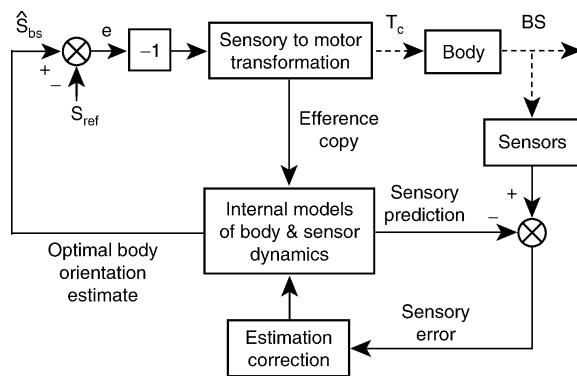
required for balance control as shown in Fig. 1. This sensory integration process includes gain factors and thresholds that effectively perform a sensory re-weighting as a function of the amplitude of the internal sensory related signals [5].

A final sensory integration scheme that has been applied to postural control is based on the engineering concepts of optimal estimation and control [7,8,9] (Fig. 4). This scheme assumes that the nervous system possesses internal models of the body and sensor dynamics. An efference copy of the motor

command generated by the postural control system is also applied to the internal model. The internal model is used to estimate body orientation and to predict the expected sensory signals associated with motor commands applied to the body. The predicted sensory signals are compared to the actual sensory signals and any sensory error is used to improve the estimate of body orientation. This improved orientation estimate is used to generate corrective motor responses via feedback control. Furthermore, this optimal estimation and control scheme is able to account for the noise



Posture – Sensory Integration. Figure 3 A sensory integration scheme based on an internal reconstruction of external physical variables. In this example, a neural representation of foot in space orientation, S_{fs} , is formed by combining graviceptive sensory information signaling body in space orientation, S_{bs} , and proprioceptive sensory information signaling body orientation relative to the feet, S_{bf} . These three sensory signals are combined to form an overall orientation signal, $\hat{S}$, which is used to generate corrective torque, T_c . The boxes labeled G_1 and G_2 are multiplying factors, T_p is a position related threshold, and T_v is a velocity related threshold. These multiplying factors and thresholds produce a change in $\hat{S}$ as a function of the amplitude and frequency of the sensory signals and effectively perform a re-weighting of these signals. See [5] for details.



Posture – Sensory Integration. Figure 4 A block diagram representation of a sensory integration scheme for postural control based on optimal estimation of sensory orientation information. An optimal estimate of body orientation in space, $\hat{S}_{bs}$, is used to generate a corrective torque, T_c , via a sensory to motor transformation process. The block with -1 indicates a sign inversion such that a positive value of e produces a negative T_c , which tends to drive the body back toward an upright orientation. The optimal orientation estimate is derived via a process that accounts for the dynamic characteristics of the body and the various sensory systems that contribute information related to body in space orientation, BS . The *dashed lines* connecting boxes indicate physical variables and the *solid line* represents neural signals.

properties and dynamic characteristics of sensory and motor systems. Modifications of this scheme can also be used to generate internal estimates of external perturbations [9]. These optimal estimation and control models have been successful in predicting a variety of experimentally observed phenomena including the

apparent sensory re-weighting that occurs in response to external perturbations of varying amplitude [9] and changes in the statistical properties of spontaneous sway caused by exposure to environments which limit access to accurate sensory orientation information [8].

Summary

The maximum likelihood principle provides an excellent foundation for understanding why the nervous system would benefit from using a weighted combination of sensory information when more than one sensory source is available. However, when sensory information is used for motor action, the physics of the body and its interaction with the environment place additional constraints on the sensory integration process. Sensory re-weighting and combined use of kinematic and kinetic sensory information provide a flexible mechanism for minimizing the effects of external disturbances while maintaining stability. Relatively simple models based on sensory reconstruction and re-weighting via threshold operations account for a wide variety of experimental data. Optimal estimation methods, developed for engineering applications and applied to postural control, also account for many experimentally observed features of sensory integration. The actual neural mechanisms for sensory integration remain to be determined.

References

1. Ernst MO, Banks MS (2002) Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* 415:429–433
2. Peterka RJ (2002) Sensorimotor integration in human postural control. *J Neurophysiol* 88:1097–1118
3. Peterka RJ, Loughlin PJ (2004) Dynamic regulation of sensorimotor integration in human postural control. *J Neurophysiol* 91:410–423

4. Cenciari M, Peterka RJ (2006) Stimulus-dependent changes in the vestibular contribution to human postural control. *J Neurophysiol* 95: 2733–2750
5. Maurer C, Mergner T, Peterka RJ (2006) Multisensory control of human upright stance. *Exp Brain Res* 171: 231–250
6. Mergner T (2002) The matryoshka dolls principle in human dynamic behavior in space: a theory of linked references for multisensory perception and control of action. *Curr Psychol Cogn* 21:129–212
7. Carver S, Kiemel T, van der Kooij H, Jeka JJ (2005) Comparing internal models of the dynamics of the visual environment. *Biol Cybern* 92:147–163
8. Kuo AD (2005) An optimal state estimation model of sensory integration in human postural balance. *J Neural Eng* 2:S235–S249
9. van der Kooij H, Jacobs R, Koopman B, van der Helm F (2001) An adaptive model of sensory integration in a dynamic environment applied to human stance control. *Biol Cybern* 84:103–115

Posture-Movement Problem

Definition

The problem of how the nervous system prevents the posture-stabilizing mechanisms from generating resistive forces when an active movement from an initial to a final posture is produced.

► Equilibrium Point Control

Posture Role of Cerebellum

DAGMAR TIMMANN

Department of Neurology, University of Duisburg-Essen, Essen, Germany

Definition

The cerebellum is critical for motor coordination and motor learning. The cerebellum is involved both in voluntary movement control, for example upper limb coordination, and postural control.

► **Ataxia** of stance and gait are characteristic signs of cerebellar disease. Cerebellar disorders result in enhanced postural sway. As a compensatory response, the stance is overly wide based. If the subject attempts to stand on a narrow base, there is increase in postural sway and a tendency to fall (Fig. 1).

Many features of cerebellar gait are related to balance disorders and ways to compensate for them. For example, step length is decreased and step width is increased. Furthermore, the coordination between posture and rhythmic movements of locomotion is impaired. Likewise, postural adjustments are disordered prior to voluntary limb movements.

This chapter focuses on findings of disordered postural control during quiet stance and in response to balance disturbances in subjects with cerebellar lesions. Localizing signs of postural disturbances in cerebellar disease are reviewed first. Next, physiology and pathophysiology of cerebellar postural control is discussed.

Description of the Theory

The structure of the cerebellar cortex is the same all over the cerebellum. Various parts of the cerebellum differ in function because of differences in fiber connections. The cerebellar cortex receives afferent input from many parts of the peripheral and central nervous system. Proprioceptive and vestibular afferents are of particular importance in cerebellar control of posture. These sensory informations are relayed to different parts of the cerebellum and probably related to different aspects of postural control.

The relative simplicity and quasicrystalline microstructure of the cerebellar cortex suggests a common computational function of this structure. As yet there is no unifying theory for cerebellar function. A number of theories and models have been proposed, including the coordination of movement across different joints, timing, an internal model for sensorimotor control or the cerebellum as a motor learning machine. These possibilities are not mutually exclusive. In the following, references to current theories of cerebellar function are made where applicable.

Functional Compartmentalization

Gross subdivision of the cerebellum into the lateral hemispheres and medial vermis gives a first idea of functional localisation within the cerebellum. The vermis is involved in the control of posture and equilibrium as well as eye movements. The hemispheres are involved in motor execution and planning of voluntary movements. Lesions of the vermis result in disturbances of stance, gait, and ocular movements, whereas lesions of the cerebellar hemispheres primarily affect limb movements.

On the basis of the efferent projections from the cerebellar cortex to the cerebellar nuclei the cerebellum has been subdivided into a medial zone (that is the vermis) projecting to the fastigial nuclei, an intermediate zone projecting to the interposed nuclei and a lateral zone projecting to the dentate nucleus. Animal lesion studies show that lesions of the fastigial nuclei are followed by impaired or prevented sitting,



Posture Role of Cerebellum. Figure 1 Ataxia of stance in a cerebellar subject suffering from spinocerebellar type 6 (SCA6). a Stance is wide-based. b If the subject attempts to stand on a narrow base, balance is lost (c) and subject has to make use of the wall to prevent a fall (d).

standing and walking, because of falls to the side of the lesion. This was interpreted as a deficit in equilibrium [1]. Efferents from the fastigial nuclei project to the brain stem and modify vestibular and reticular influences on posture.

The flocculonodular lobe and adjoining parts of the caudal vermis have been named the **▶vestibulocerebellum** because of heavily projecting vestibular afferents. Lesions of the vestibulocerebellum cause postural ataxia of head and trunk during sitting, standing and walking. Patients frequently fall while sitting. The classic example is medulloblastoma, which occurs most often in the cerebellum in children between 5 and 10 years of age. In subjects with such lesions, visual stabilization of posture, as evaluated by comparing sway with eyes

closed and sway with eyes open, is impaired (absence of **▶Romberg's sign**). Severe postural sway is present with eyes open and is essentially unchanged with eyes closed. Intersegmental movements are diminished.

The anterior and posterior parts of the vermis and paravermal parts of the cerebellar hemispheres are called the **▶spinocerebellum** because of their spinal afferents. Damage to the spinocerebellar parts of the **▶anterior lobe** is characterized by ataxia of stance and gait. The classic example is alcoholic cerebellar degeneration. Visual stabilization of posture is relatively preserved and the tremor is provoked by eye closure (presence of Romberg's sign). Patients rarely fall because the body tremor is opposite in phase in head, trunk, and legs, resulting in a minimal shift of the center of gravity.

Chronic damage to the lateral cerebellar hemispheres that is the cerebro- or pontocerebellum, does not result in significant postural disorders. The lateral hemispheres receive the main input from the cerebral cortex, synaptically interrupted in the pontine nuclei.

Diener and coworkers [2] measured body sway by means of a force-measuring platform in human subjects with lesions of the ponto-, vestibulo- or spinocerebellum (Fig. 2).

Postural sway was basically unaffected in subjects with lesions of the lateral cerebellar hemispheres. Lesions of the lower vermis caused omnidirectional postural sway with frequency components below 1 Hz. Lesions of the anterior lobe led to anterior-posterior body sway with a frequency of about 3 Hz. A more recent human lesion study questioned if 3 Hz body oscillations occur exclusively in lesions of the anterior lobe. Likewise, assessment of trunk sway in patients with spinocerebellar ataxias showed that postural instability was generally more pronounced in the pitch than in the roll plane, corresponding with predominant involvement of the spinocerebellum [3].

Posture Role of the Spinocerebellum

Postural muscle tone is a primary contributor to the maintenance of upright stance. Damage to the anterior lobe in experimental animals primarily produces a change of muscle tone. In decerebrate animals, the decerebrate rigidity increases, as do the postural reflexes. In humans it is doubtful whether lesions of the anterior lobe produce increased muscle tone. Postural sway following lesions of the anterior lobe has been explained by an increased gain of posturally stabilizing (long loop) reflexes [4].

Sway can be provoked by platform perturbations or electrical stimulation of the tibial nerve. Subjects with anterior lobe atrophy show hypermetric postural responses and overshooting of the initial posture, with

larger than normal surface reactive torque responses and exaggerated and prolonged muscle activity (Fig. 3; [5]).

Latencies of postural responses provoked by platform perturbations are normal in patients with cerebellar disorders. Increased gain and prolonged duration of ▶long loop reflexes result in an overcompensation of the postural tasks and are believed to evoke (exaggerated) postural responses of the corresponding antagonists. The postural tremor supposedly continues by the same mechanism.

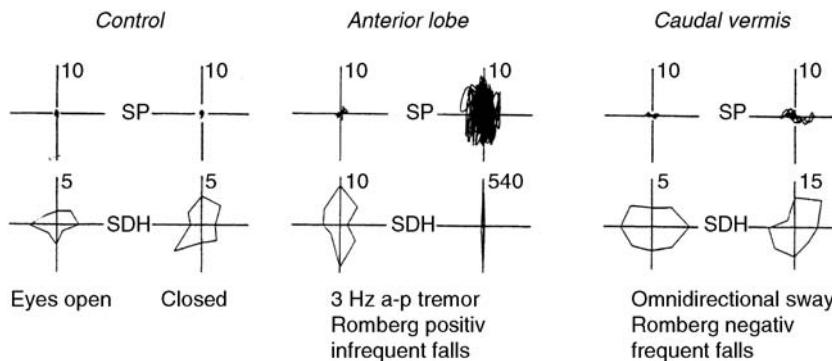
A more recent model of the (spino-) cerebellum supports the notion that the cerebellum may contribute to balance by long loop feedback with scheduling of linear gains at the same joint and interjoint responses between ankle, knee, and hip [6]. Explicit internal dynamics models within the cerebellum, which have been hypothesized to control voluntary limb movements, do not necessarily contribute to spinocerebellar balance control.

Posture Role of the Vestibulocerebellum

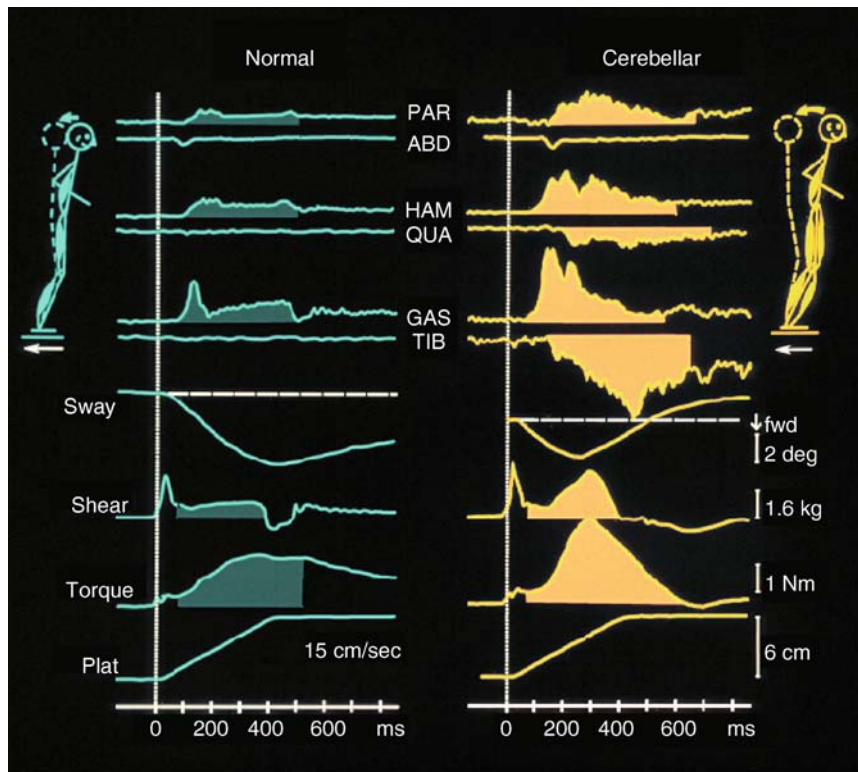
Studies in primates have helped to understand the specific contributions of the vestibulocerebellum to postural control. Knowledge based on human studies is more limited.

The dominant afferent inputs to the vestibulocerebellum come from the semicircular canals, which signal changes in head position, and the otolith organs, which signal the orientation of the head with respect to gravity. Semicircular canal information is relayed to the flocculus and otolith information to the caudal cerebellar vermis (▶nodulus and ▶uvula).

Sensory input from the otoliths evoke vestibulocollic and vestibulospinal reflexes that maintain the head vertical with respect to gravity. Vestibulocollic and vestibulospinal reflexes are primarily static. The semicircular canals, however, have weaker influences on spinal



Posture Role of Cerebellum. Figure 2 Sway path (SP) and sway direction histograms (SDH) in a control, a patient with anterior lobe atrophy and a patient with a vestibulocerebellar lesion. Note the strong preference of anterior-posterior sway in the patient with anterior lobe atrophy. (Adapted from [2]; with permission).



Posture Role of Cerebellum. Figure 3 Mean postural responses evoked by a backward translation of the supportive platform in a control group and a cerebellar group with anterior lobe atrophy. Cerebellar subjects show hypermetric postural responses, exaggerated and prolonged muscle activity and larger than normal surface reactive torque responses. Latencies of postural responses are normal. Traces show (top to bottom): electromyographic (EMG) recordings from paraspinal (PAR), rectus abdominis (ABD), biceps femoris (HAM), rectus femoris (QUA), gastrocnemius (GAS), and anterior tibial (TIB) muscles; sway, shear forces, surface torque and platform displacement. (Adapted from [5]; with permission).

circuits and serve predominantly to control extraocular muscles and coordinate head and eye movements.

It has been assumed that a lesion of the vestibulocerebellum leads to disturbed gravitational set values and therefore to a loss of spatial orientation vs. gravity. The set value of determining the upright is lost.

More recent single cell recording studies in the primate provide evidence that the rostral fastigial nucleus represents a main processing center of otolith driven information for inertial motion detection and spatial orientation. Angelaki and coworkers [7] showed that cerebellar and brainstem motion sensitive neurons encode dynamically processed otolith signals appropriate to construct an internal model of inertial motion detection.

A study in children and adolescents with chronic surgical cerebellar lesions underscores the importance of the fastigial nuclei in human postural control. High-resolution magnetic resonance imaging allowed detailed analysis of the lesion side. The ability to control upright stance based on vestibular information alone (that is without visual information and unreliable proprioceptive information) was only impaired in

subjects with cerebellar lesions that included the fastigial nuclei (Fig. 4; [8]).

Findings further showed that the lesion site was critical for the motor recovery. Lesions affecting the cerebellar nuclei (but not the cerebellar cortex) were not compensated at any developmental age.

Interestingly, otolith dysfunction has been demonstrated in patients with spinocerebellar ataxia type 6 (SCA6). SCA6 is a hereditary disorder, which affects the vestibulocerebellum early in the disease.

Role of Cerebellum in Postural Adaptation

Many studies show that the cerebellum plays an important role in motor learning, in particular in adaptation and automatization of movement. Disordered adaptation probably contributes to ataxia of stance, but has been assessed by few studies only.

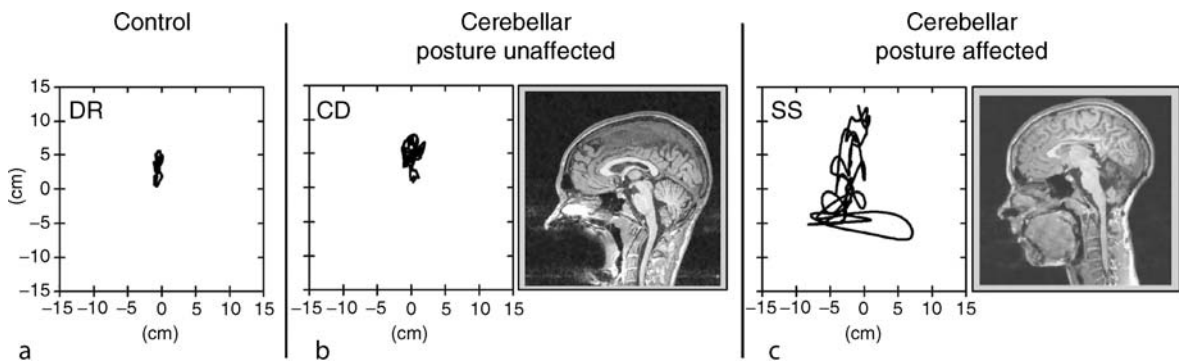
Most studies investigated adaptation of early automated postural responses to changes in surface perturbations. Because the contribution of the somatosensory system is much greater than that of the vestibular system when compensating for transient surface

perturbations, contributions of the spinocerebellum are assessed. Initial findings of Nashner [9] showed that healthy subjects but not cerebellar patients adapt automated postural responses depending on context. Nashner compared postural responses to backward translations and upward rotations. Both lead to the same ankle rotation. Upright stance however, is maintained by contraction of the anterior tibial muscle in upward rotations, but of the gastrocnemius muscle in backward translations. In controls, but not cerebellar subjects, responses that stabilize posture were facilitated progressively with repeated trials, whereas responses that destabilize posture were diminished. These findings were, however, challenged in later studies. When the type

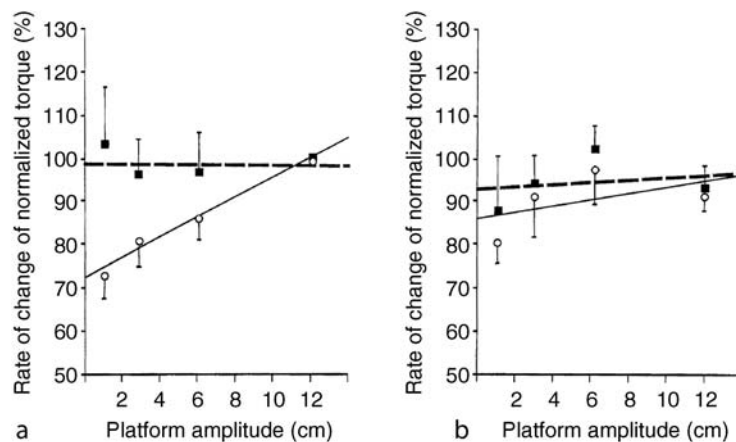
of perturbation changed from translation to rotation and vice versa both controls and cerebellar subjects showed an immediate change in the response amplitudes of the gastrocnemius and anterior tibial muscles.

Horak and Diener [5] studied whether cerebellar subjects could learn to adjust for predictable postural perturbations during standing (Fig. 5).

When different displacement amplitudes were presented in a serial (predictable) format, healthy subjects were able to appropriately scale their initial postural responses. In contrast, cerebellar subjects were unable to learn to use predictive feedforward control (in other words central set from prior experience) to scale their early automated postural responses



Posture Role of Cerebellum. Figure 4 Effects of fastigii lesions on postural sway. Postural sway is increased in patient SS, but not in patient CD compared to the control subject DR. In both patients an astrocytoma had been surgically removed. The sagittal MRI images reveal that area above the 4th ventricle, that is the location of the fastigial nuclei, was affected in SS but not in CD. Shown are the center of gravity sway paths over 20 s in a condition that is dependent on vestibular function (that is eyes closed and surface sway referenced). (Adapted from [8]; with permission).



Posture Role of Cerebellum. Figure 5 Scaling of torque responses to platform displacement amplitude in controls (*continuous line*) and cerebellar subjects (*broken line*). The mean $\pm$ SE of normalized torque responses are indicated for serial (predictable) (a) and random (b) amplitude presentation. Control subjects scale to predictable but not random presentation of displacement amplitudes, whereas the cerebellar group scaled neither to predictable or random presentation. (Adapted from [10]; with permission).

to expected perturbation amplitudes. A subsequent study showed that cerebellar patients could predict perturbation amplitudes based on prior experience, but they could not use this prediction to modify precisely the gain of early automated postural responses [10]. The spinocerebellum may be important for accurate tuning of response gain based on prediction.

Cerebellar contribution to adaptation of vestibular reflexes is likely. Cerebellar contributions have been investigated in great detail for adaptation of the vestibulo-ocular reflex (VOR). The function of the VOR is to stabilize retinal images by generating smooth eye movements that are equal and opposite to each head movement. Learning occurs whenever image motion occurs persistently during head turns; as a result image stability is gradually restored. The cerebellar role in retention is disputed, but there is a consensus on the need of an intact cerebellum (that is flocculus) for acquisition.

The role of the caudal cerebellar vermis (nodulus and uvula) for adaptation of the “static” vestibulocollic and vestibulospinal reflexes has not been assessed in detail.

Summary

The medial cerebellum (that is vermis) is of particular importance in postural control. The contribution of the cerebellum is two-fold. Vermal parts of the anterior lobe (that is spinocerebellum) are involved in control of automated postural reflexes evoked by proprioceptive feedback. Hypermetric postural responses and disordered adaptation can be explained by inaccurate tuning of reflex gain. Disordered coordination between head, trunk and legs (asynergia) probably contributes but is less well understood. Caudal parts of the vermis (that is the vestibulocerebellum) play an important role in spatial orientation of the body against gravity and detection of inertial body motion evoked by otolith feedback. The vestibulocerebellum appears to be important in building an internal model of inertial body motion.

References

1. Thach WT, Bastian AJ (2004) Role of the cerebellum in the control and adaptation of gait in health and disease. *Prog Brain Res* 143:353–366
2. Diener HC, Dichgans J, Bacher M, Gompf B (1984) Quantification of postural sway in normals and patients with cerebellar diseases. *Electroencephalogr Clin Neurophysiol* 57:134–142
3. Van de Warrenburg BP, Bakker M, Kremer BP, Bloem BR, Allum JH (2005) Trunk sway in patients with spinocerebellar ataxia. *Mov Disord* 20:1006–1013
4. Mauritz KH, Schmitt C, Dichgans J (1981) Delayed and enhanced long latency reflexes as the possible cause of postural tremor in late cerebellar atrophy. *Brain* 104:97–116
5. Horak FB, Diener HC (1994) Cerebellar control of postural scaling and central set in stance. *J Neurophysiol* 72:479–493
6. Jo S, Massaquoi SG (2004) A model of cerebellum stabilized and scheduled hybrid long-loop control of upright balance. *Biol Cybern* 91:188–202
7. Angelaki DE, Shaikh AG, Green AM, Dickman JD (2004) Neurons compute internal models of the physical laws of motion. *Nature* 430:560–564
8. Konczak J, Schoch B, Dimitrova A, Gizewski E, Timmann D (2005) Functional recovery of children and adolescents after cerebellar tumour resection. *Brain* 128:1428–1441
9. Nashner LM (1976) Adapting reflexes controlling the human posture. *Exp Brain Res* 26:59–72
10. Timmann D, Horak FB (1997) Prediction and set-dependent scaling of early postural responses in cerebellar patients. *Brain* 120:327–337

Posturography

Definition

Analysis of body posture, and postural control, typically using computerized image analysis of the position and movement of body segments over time.

Potential Energy

Definition

Certain systems of forces (called conservative systems) are such that the forces can be obtained as (minus) the spatial derivatives of a single scalar function of position. This function, if it exists, is called the potential energy of the system. It is of paramount importance in analytical mechanics.

► Mechanics

Potentiation

Definition

Potentiation refers to the combination of two stimuli resulting in a larger response than the sum of responses to each stimulus alone.

Potentiometer

Definition

A variable resistor used to control an electronic device.

► [Hearing Aids](#)

Power

Definition

Power is the amount of energy produced per unit time. The mechanical power a skeletal muscle produces is the product of the force in the muscle and the velocity of the muscle.

Power Density Spectrum

Definition

A power density spectrum is a plot of the power (watts) in a signal as a function of frequency; also referred to as the autospectrum. Fast Fourier transform is used most commonly to construct the power density spectrum.

► [Signals and Systems](#)

Power Stroke

Definition

The power stroke of the cross-bridge cycle is the phase of force production. In the current cross-bridge thinking, the power stroke is initiated by the release of the free phosphate from ATP hydrolysis.

► [Sliding Filament Theory](#)

PPAR γ

Definition

Peroxisome proliferator-activated receptors act as ligand-activated transcription factors, similar to other nuclear hormone receptors. One of its isoforms, PPAR γ , exerts anti-inflammatory activities in brain cells by reducing proinflammatory cytokines.

► [Neuroinflammation: Chronic Neuroinflammation and Memory Impairments](#)

p55-R

► [Brain Inflammation: Tumor Necrosis Factor Receptors in Mouse Brain Inflammatory Responses](#)

Praxis Navigation Strategy

Definition

Behavior relying on an egocentric reference frame and directed by a specific motor sequence to get a goal location.

► [Spatial Memory](#)

PRC

► [Phase Response Curve](#)

Pre-Bötzing Complex

Definition

A physiologically defined region within the ventrolateral medulla of mammals that is critical for the

generation of inspiratory activity. The pre-Bötzinger complex can be functionally isolated in brainstem slice preparations, and is still capable of generating three specific rhythmic activities that have many characteristics of normal respiratory activity (eupnea), gasping and sighing.

►PreBötzinger Complex Inspiratory Neurons and Rhythm Generation

Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation

CHRISTOPHER A. DEL NEGRO, JOHN A. HAYES, RYLAND W. PACE

The Department of Applied Science, The College of William and Mary, Williamsburg, VA, USA

Definition

The ensemble of neurons in the ventral medulla that plays an important role in generating breathing behavior in mammals by synchronously producing large-magnitude bursts that drive the inspiratory phase of the respiratory cycle.

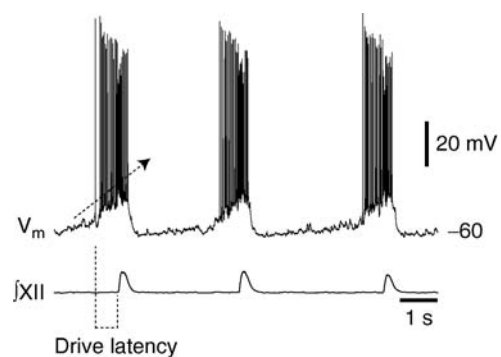
Characteristics

The ►preBötzinger Complex (preBötC) of the ventral medulla plays an important role in generating breathing behavior in mammals. Anatomical studies have demarcated the borders of the preBötC and experiments in vivo have defined its functional purview. However an unsolved problem pertains to which neurons – and which intrinsic and synaptic properties – make up the rhythmogenic kernel? In vitro models of respiration, particularly slice preparations from neonatal rodents, make experimental tests possible. Transverse slices isolate the preBötC and provide unprecedented access to preBötC neurons for electrophysiology and imaging while maintaining spontaneous inspiratory motor activity, which can be monitored via the ►hypoglossal (XII) cranial nerve root. A diverse array of intrinsic and synaptic properties have been found, which subsequently motivated numerous attempts to subdivide preBötC neurons into various ‘types’ to assign roles in respiratory rhythm generation. Here we review and critique these classification schemes and proffer objective criteria to distinguish rhythmogenic neural properties.

Inspiratory Drive Latency and Peptide Receptors

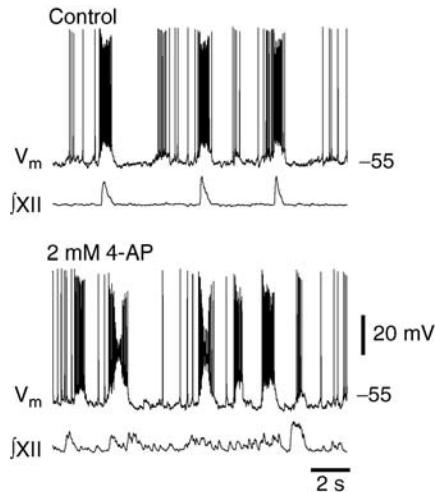
Rekling and colleagues [1] proposed a classification scheme that considered sensitivity to ►neuropeptides and ►inspiratory drive latency, defined as the time interval consisting of a crescendo of EPSPs and spiking activity preceding XII motor output (Fig 1). They argued that inspiratory neurons with the earliest drive latency and highest levels of excitability, which also responded to inspiratory drive latency that modulate respiratory rhythm, were most likely to be rhythmogenic. Earliest to activate were type 1 neurons with ~400 ms drive latency and highly excitable membrane properties. Type 2 neurons also exhibited high excitability with ~170 ms drive latency. The least excitable were type 3 neurons with drive latency of ~100 ms. Type 1 neurons were proposed to be rhythmogenic and to activate type 2 neurons downstream, followed by type 3, which were postulated to have a motor or premotor function.

Transient K^+ current, i.e., A-current (I_A), was expressed exclusively in type 1 neurons whereas the hyperpolarization-activated mixed cation current (I_h) was associated only with type 2 neurons. These data suggested a genuine disparity that could distinguish a hierarchy of rhythmogenic subtypes. We measured I_A in ~60% of preBötC inspiratory neurons and found that its selective blocker, 4-aminopyridine (2 mM), caused profound disruptions in the respiratory rhythm (Fig 2), consistent with the proposal that I_A expression is a hallmark of rhythmogenic neurons (i.e., type 1-like). I_h is present in ~15% of preBötC inspiratory neurons and blocking it with Cs^+ or organic agents speeds up the rhythm, which is consistent with I_h expression



Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation. Figure 1

A typical voltage trajectory for a preBötC neuron putatively involved in rhythm generation shown with respiratory-related XII motor output. Inspiratory drive latency is illustrated with dotted lines to mark the onset of inspiratory drive and the XII motor discharge. A dotted-line arrow emphasizes the incremental depolarization and spike discharge pattern that distinguish relatively small neurons with early drive latency.



Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation. Figure 2 Pharmacological blockade of I_A disrupts respiratory rhythm *in vitro*. The preBötC neuron in control showed early inspiratory drive latency and spike discharge as well as robust inspiratory bursts. After 2 mM 4-AP application the respiratory rhythm was erratic and noisy, and the inspiratory neuron generated bursts that were not necessarily associated with a collective inspiratory burst at the XII motor output level. Blockade of I_A furthermore increased inspiratory burst amplitude to such an extent that spiking activity inactivated transiently.

in neurons that may also be rhythmogenic, but not preeminent (i.e., type 2-like).

Whether I_A and I_h expression maps one-to-one with differences in drive latency, thus validating the type 1 versus 2 classification scheme, has not yet been resolved. Our measurements revealed a continuous drive latency distribution with a mean of ~ 300 ms (Fig. 3a), rather than bimodal with peaks at ~ 200 and ~ 400 ms, as originally suggested. Therefore, types 1 and 2 could reflect the same underlying population of rhythmogenic neurons, but neurons with I_A may be more important for rhythmogenesis simply because I_A plays a more important role than I_h in rhythmogenesis (Fig. 2).

Rekling's classification scheme recognized peptide sensitivity as a criterion to distinguish rhythmogenic neurons. In a watershed study, Gray *et al.* showed that ▶neurokinin-1 receptor (NK1R) expression demarcated the borders of the preBötC and that ▶substance P (SP), the endogenous ligand for NK1Rs, directly excited rhythmogenic neurons, i.e., with properties consistent with types 1 and/or 2, and also profoundly excited respiratory rhythm [1]. These results led to the hypothesis that NK1R-expressing (NK1R⁺) neurons, distinct by anatomical and physiological criteria, comprised the rhythmogenic kernel in the preBötC. In support of this hypothesis, ablation of NK1R⁺ neurons

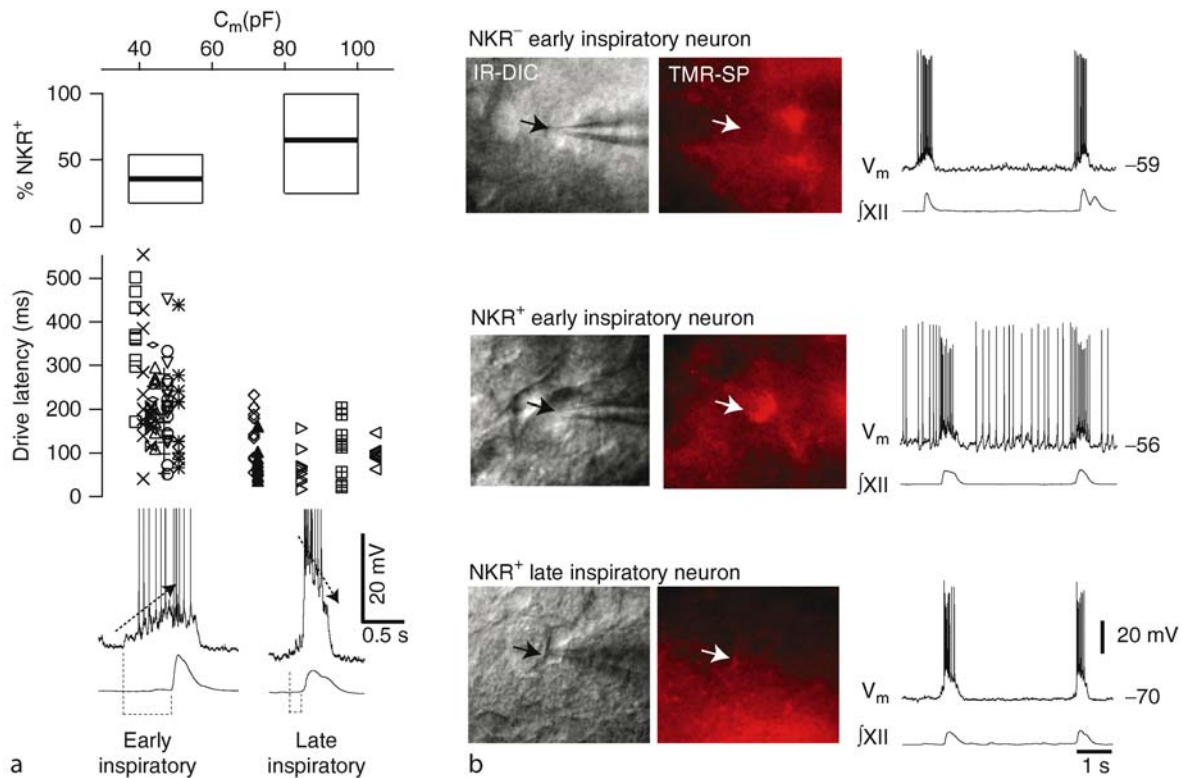
in awake intact adult rats abolishes normal breathing behavior [3].

Guyenet and colleagues used *in vivo* electrophysiology and neuroanatomy to show NK1R⁺ neurons concentrated in a region coextensive with the preBötC, where there was an abundance of inspiratory neurons and few ▶expiratory neurons [4]. Inspiratory neurons with early drive latency *in vivo* could be antidromically activated from the contralateral medulla 70% of the time, consistent with interneurons in a local circuit. 34% of these early inspiratory neurons were NK1R⁺, whereas expiratory or phase-spanning neurons did not appear to have the NK1R (i.e., NK1R⁻). These data are consistent with the idea that drive latency and peptide receptor expression might specify rhythmogenic neurons in the preBötC.

NK1R⁺ neurons in the preBötC showed no immunoreactivity for tyrosine hydroxylase (TH) nor choline acetyl-transferase (ChAT) [4]. Therefore, these neurons were unlikely to be catecholaminergic or cholinergic (motoneurons). As a control against these negative findings in NK1R⁺ neurons of the preBötC, co-labeled NK1R⁺/TH⁺ neurons were found in the noradrenergic A5 and C1 regions outside the preBötC and NK1R⁺/ChAT⁺ motoneurons were profusely labeled in the ▶nucleus ambiguus [1,4]. The NK1R⁺ neurons in the preBötC area rarely showed immunoreactivity to GAD67 or GlyT2, which would have distinguished them as GABAergic or glycinergic inhibitory neurons, and were later shown to contain vesicular glutamate transporter mRNA. In sum, NK1R⁺ neurons concentrated in the preBötC are locally interconnected excitatory interneurons that discharge prior to the onset of the inspiratory phase, hallmark properties for a role in rhythmogenesis (Fig. 3b).

But the hypothesis that NK1R⁺ neurons define the kernel needs to be reevaluated because the NK1R⁺ population can be subdivided. The smallest NK1R⁺ neurons express preprosomatostatin mRNA, do not project to the spinal cord, nor express preproenkephalin (PPE) mRNA, and are rostrally sited in the preBötC area [5]. 75% of these NK1R⁺ neurons project contralaterally and may be co-extensive with the NK1R⁺ cells whose destruction abolishes normal breathing [3]. However, much larger NK1R⁺ neurons found in the caudal preBötC area express PPE mRNA and project to the spinal cord, consistent with a premotor role, not rhythmogenesis [5].

Combining whole-cell patch clamp with a fluorescent labeling technique that tags all SP-sensitive NK1R⁺ neurons, we found rhythmogenic properties, e.g., early drive latency, small size, in NK1R⁺ neurons (Fig. 3b). Early drive latency (~ 300 ms, type 1- or type 2-like) was associated with small preBötC inspiratory neurons ($C_M \sim 45$ pF) of which 36% were NK1R⁺. In contrast, larger preBötC inspiratory neurons ($C_M \sim 86$ pF)



Pre-Bötzing Complex Inspiratory Neurons and Rhythm Generation. Figure 3 Criteria to distinguish inspiratory preBötC neurons that are involved in rhythm generation. (a), Inspiratory drive latency (lower ordinate) and neurokinin receptor (NKR) expression (upper ordinate) are plotted as a function of whole-cell capacitance C_m . Box plots show mean and 95/5% credible interval range. Typical examples of early as well as late inspiratory phenotypes are shown beneath their characteristic C_m range. (b), NKR expression is shown for three typical inspiratory preBötC neurons. Two early inspiratory neurons, which are hypothesized to be rhythmogenic on the basis of membrane properties, are shown with NKR expression (NKR⁺) and without (NKR⁻). An NKR⁺ late expiratory neuron, hypothesized to have motor or premotor function, is also illustrated. Modified from [2].

showed drive latency of ~ 100 ms and were NKR⁺ 67% of the time (Fig. 3). The majority of the preBötC neurons we recorded were small with early inspiratory activity. The early latency, small size, and incremental discharge trajectory are characteristic of glutamatergic interneurons, and resemble types 1 and 2 [1] and therefore are probably glutamatergic, not GABA- or glycinergic neurons [4]. The fraction of NKR⁺ neurons with early drive latency in adult rats in vivo is also near 36%, so the fraction of NKR⁺ neurons in the preBötC appears consistent in neonate and adult rodents.

Large preBötC inspiratory neurons that activate latest in the respiratory cycle (Fig. 3a) may be premotor neurons [5]. A large fraction of these cells were NKR⁺ (Fig. 3b) thus sensitive to saporin lesions [3]. However, because the small neurons with early drive latency are more numerous saporin lesions will probably cause a greater total reduction in NKR⁺ rhythmogenic-like neurons. However, the destruction of a large fraction of NKR⁺ respiratory premotoneurons must be considered

as a factor in explaining apneas resulting from saporin lesions [3].

Finally, we showed that peptide sensitivity and receptor expression were not necessarily synonymous. Even though only 36% of the putatively rhythmogenic neurons were NKR⁺, a much larger fraction (87%) showed a SP-evoked inward current (I_{SP}) in voltage clamp, which suggests that gap junctions may provide a means for NKRs to evoke inward current in both NKR⁺ as well as NKR⁻ preBötC inspiratory neurons [2]. This suggests that most of the putatively rhythmogenic neurons still satisfy the three objective criteria: small size, early inspiratory drive latency, and peptide sensitivity.

Pacemaker Properties: Not Specialized Phenotypes, Cannot Explain Rhythmogenesis

Evidence for a pacemaker cell-type accompanied the discovery of the preBötC [6]. In the absence of synaptic transmission, some neurons with a baseline

membrane potential between -57 and -45 mV spontaneously depolarize and generate rhythmic bursts, dubbed ►**conditional pacemaker properties**. Voltage-dependent pacemaker properties were attractive from the standpoint of rhythmogenesis because conditional bursting in isolated cells had the same duty cycle as the network-intact XII rhythm. Pacemaker neurons were postulated to form a specialized phenotype that periodically excites so-called follower neurons and synchronizes both sets of neurons through excitatory synaptic interconnections.

PreBötC inspiratory neurons have been classified as either pacemakers or followers, yet this binary classification is more apparent than real. Voltage-dependent bursting depends on a requisite region of negative slope in the current-voltage relationship endowed by ►**persistent Na^+ current** (I_{NaP}). We now know that I_{NaP} is a generic property, ubiquitously expressed throughout the preBötC and ventral medulla. Since baseline membrane potential must be within a specific voltage window, ►**leakage potassium current** ($I_{\text{K-Leak}}$) also becomes important to maintain voltage-dependent bursting. I_{NaP} and $I_{\text{K-Leak}}$ are distributed continuously among preBötC inspiratory neurons, thus a small subset with conditional bursting properties arises naturally for neurons with the proper $I_{\text{NaP}}/I_{\text{K}}$ ratio and is a byproduct of heterogeneity in membrane properties.

The real question is whether I_{NaP} is important for rhythmogenesis. To avoid caveats associated with bath-applications [7], we performed micropressure injections to apply riluzole – and low doses of TTX (20 nM) that preferentially block I_{NaP} – directly into the preBötC without affecting premotor or XII motoneurons (Fig. 4). Riluzole and 20 nM TTX microinjections did not stop the rhythm nor affect XII motor output, indicating that I_{NaP} is not obligatory for rhythmogenesis [8].

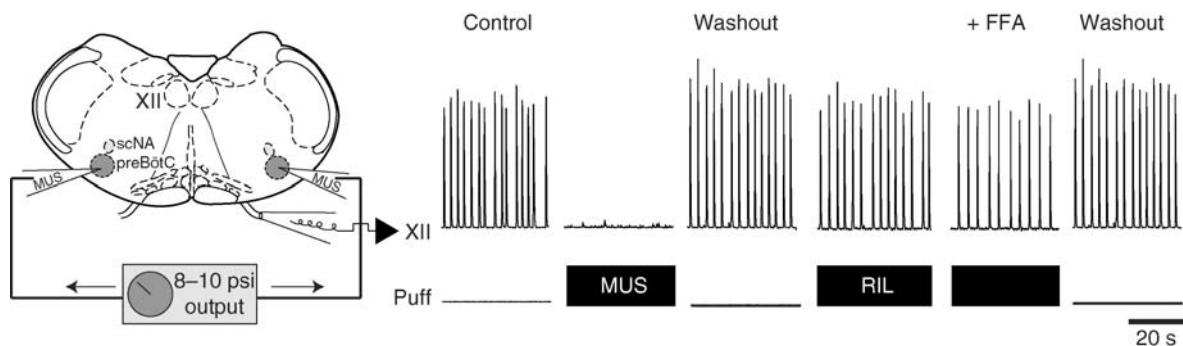
Voltage-dependent pacemaker properties do not constitute a specialized phenotype in the preBötC because I_{NaP} is commonplace and nonessential for rhythmic function. Nevertheless, I_{NaP} contributes to baseline membrane potential and facilitates high-frequency spiking, and thus helps maintain neural excitability [7,8].

Pacemaker properties unrelated to I_{NaP} were documented in 2001. Bursting was sensitive to blockade by Cd^{2+} , indicating dependence on intrinsic Ca^{2+} currents; later a ► **Ca^{2+} -activated nonspecific cation current** (I_{CAN}) was shown to be involved [17,20]. Cd^{2+} -sensitive bursting neurons were posited to form an additional rhythmogenic subpopulation that could drive rhythmogenesis in combination with, or in lieu of, I_{NaP} pacemaker neurons [9]. However, two key facts falsify this hypothesis: first, Cd^{2+} -sensitive pacemaker properties are sparse or nonexistent in early in post-natal development [9], yet riluzole does not stop the rhythm. Second, doses of flufenamic acid (FFA, 10–100 μM) that attenuate I_{CAN} to an extent that precludes Cd^{2+} -sensitive bursting – but do not completely block I_{CAN} – do not stop rhythmogenesis in the presence of riluzole or TTX at any post-natal age [8].

Unless a miniscule number of pacemaker neurons that are insensitive to I_{NaP} and I_{CAN} antagonists can drive the rhythm – or a heretofore undiscovered pacemaker phenotype exists – these observations invalidate the hypothesis that pacemaker neurons are the basis for rhythmogenesis.

I_{CAN} Activates Synaptically and Generates Rhythmic Inspiratory Bursts in PrebötC Neurons

►**AMPA receptors** (AMPA) are necessary for rhythmogenesis. Moreover, group I ►**metabotropic glutamate receptors** (mGluRs) and ►**NMDA receptors**



Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation. Figure 4 Sequential drug application experiments using local microinjection of 10 μM riluzole (RIL). Top traces show XII motor output, lower traces labeled “puff” reflect TTL pulses at 3 Hz that gate micropressure drug-delivery injections. Bilateral injection of 15 μM muscimol (MUS) is used to verify the effective microinjection pipette locations. After recovering from MUS, RIL is microinjected for >20 min, followed by bath application of 100 μM flufenamic acid (FFA). The rhythm did not stop, nor became perturbed in any noticeable form, after >20 min of bath-applied FFA (cumulative RIL exposure >40 min). Recovery from all drugs occurred within 1–2 h and is shown as washout. Modified from [8].

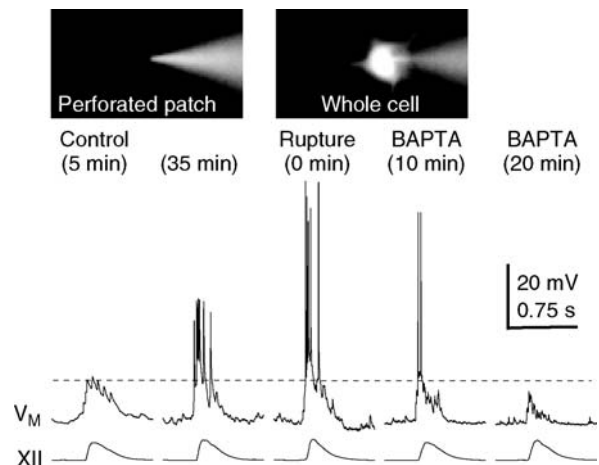
(NMDARs) provide a substantial – yet heretofore unrecognized – contribution to generating inspiratory bursts and rhythm. Both ionotropic, and metabotropic glutamate receptors activate I_{CAN} via voltage-gated Ca^{2+} channels and inositol (1,4,5)-triphosphate (IP_3)-mediated intracellular Ca^{2+} release. Additionally, I_{CAN} serves to generate robust inspiratory drive potentials in all preBötC inspiratory neurons [10].

Group I mGluRs consist of subtypes mGluR1 and mGluR5. While mGluR5 triggers I_{CAN} activation, via IP_3 -mediated intracellular Ca^{2+} release, mGluR1 appears to promote inspiratory drive potentials by transiently closing K^+ channels. In contrast, group II mGluRs modulate interburst period but do not contribute to inspiratory burst generation.

Ca^{2+} influx via NMDARs may also contribute to I_{CAN} activation. AMPAR-mediated depolarization recruits **voltage-gated Ca^{2+} channels** and may partially relieve the voltage-dependent Mg^{2+} block of NMDARs and thus indirectly activate I_{CAN} in the preBötC. This is the first example of a convergent activation of I_{CAN} involving NMDARs, Ca^{2+} channels and intracellular Ca^{2+} release to serve burst generation in a **central pattern generator**.

How important is I_{CAN} ? We used two strategies to test its role. In the first, intracellular drug application was employed to test the role of I_{CAN} in drive potential generation in a single preBötC neuron without disrupting respiratory rhythm in the rest of the network. We recorded inspiratory drive in control using **perforated patches** (Fig. 5), which does not modify the intracellular milieu. Then we ruptured the patch and dialyzed the cytosol with patch solution containing 30 mM BAPTA, a high-affinity Ca^{2+} chelator. BAPTA abolishes the ability to activate I_{CAN} and reduced drive potentials by 70% after ≥ 20 min suggesting I_{CAN} that I_{CAN} is the major charge carrier underlying inspiratory drive potentials [10].

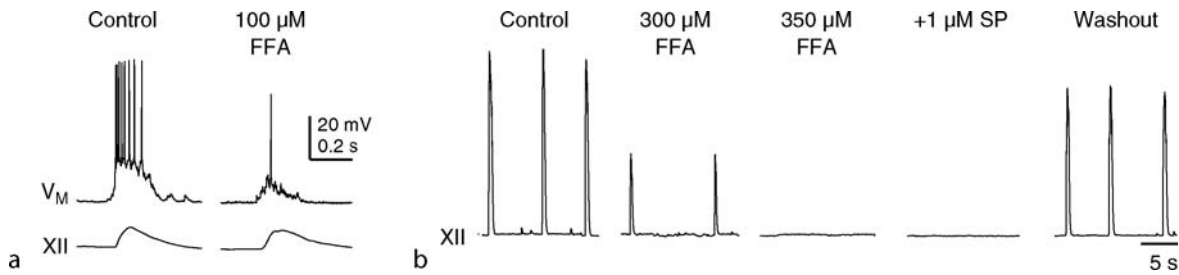
We examined whether I_{CAN} (Fig. 6) was crucial for rhythmogenesis in the network as a whole using bath application of the selective antagonist flufenamic acid (FFA). Dose is a critical issue: 100 μM FFA incompletely blocks I_{CAN} and does not stop the network rhythm, but nonetheless reduces inspiratory drive potentials by $\sim 40\%$ [10]. Higher concentrations of FFA (300–350 μM) stop respiratory rhythmogenesis. While an attractive conclusion is that FFA at ≥ 300 μM stops rhythmogenesis by fully and selectively blocking I_{CAN} , FFA doses exceeding 100 μM exert numerous side effects [10], and thus confound such a straightforward interpretation. Nevertheless, we can conclude that I_{CAN} contributes enormously to inspiratory drive on a cycle-to-cycle basis by transforming synaptic input into long-lasting membrane depolarization, and thus plays an important role in inspiratory burst generation.



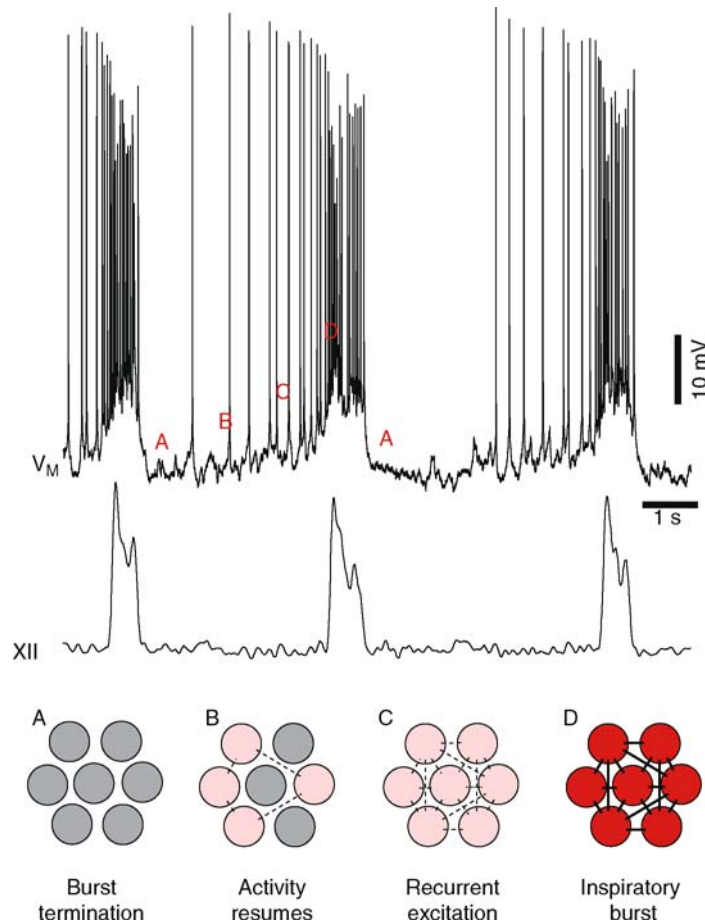
Pre-Bötzing Complex Inspiratory Neurons and Rhythm Generation. Figure 5 Perforated-patch control recordings and subsequent intracellular dialysis with 30 mM BAPTA patch solution demonstrate the importance of Ca^{2+} transients and I_{CAN} . Control conditions were recorded in the perforated-patch configuration (5 and 35 min shown). BAPTA was introduced into the cytosol via patch rupture (0 min) and caused a progressive attenuation of the drive potential. Baseline membrane potential was -60 mV throughout the experiment. The perforated-patch configuration (PP; left picture) is confirmed by the failure of the Lucifer yellow in the patch-pipette solution to dialyze the cell. The whole-cell configuration (WC; right picture) allows Lucifer yellow to fill the cell. The V_M traces verify that the underlying inspiratory drive potential can be accurately measured in PP mode as compared to the first minute of WC mode. In WC, the spikes are less truncated because the access impedance decreases. Modified from [10].

The Group-Pacemaker Hypothesis of Respiratory Rhythm Generation

I_{CAN} activation depends on AMPA, NMDA, and metabotropic glutamate receptors during endogenous respiratory behavior, and thus is properly considered a network property. The group-pacemaker hypothesis (Fig. 7) postulates a mechanism for rhythmogenesis wherein recurrent synaptic excitation linked to postsynaptic intrinsic currents plays a special role. In the group pacemaker, a fraction of neurons in the preBötC are spontaneously firing; baseline voltage during the expiratory phase exceeds spike threshold. In the waning expiratory phase, active neurons excite silent neurons, which in turn excite additional silent neurons and also provide positive feedback to re-excite the neurons already spiking. I_{CAN} is normally latent and unavailable except when recruited by synaptic excitation. Glutamatergic input sufficient to evoke I_{CAN} is ultimately achieved a few hundred milliseconds prior to inspiratory burst discharge. The negative feedback process that causes burst termination remains unknown. After burst termination, neurons



Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation. Figure 6 Effects of I_{CAN} antagonist flufenamic acid (FFA) on inspiratory bursts and rhythmogenesis. (a), Typical inspiratory bursts recorded in whole-cell conditions for control and 100 μ M FFA, respectively. (b), An experiment showing that 300 μ M FFA severely perturbed the respiratory rhythm (monitored via XII discharge) and 350 μ M FFA stopped it altogether. In the presence of 350 μ M FFA, even the excitatory peptide substance P (which normally stimulates rhythmogenesis profoundly) fails to revive rhythm generation. The effects of FFA were reversible, as shown by the full recovery in washout conditions. Modified from [10].



Pre-Bötzinger Complex Inspiratory Neurons and Rhythm Generation. Figure 7 Group-pacemaker hypothesis of rhythm generation. The membrane potential of an inspiratory preBötC neuron is shown (V_M) with XII motor output. Images at the bottom depict neuronal activity at different stages of the cycle. (a), the refractory state following the inspiratory burst. (b), some preBötC neurons recover their excitability and begin to spike low rates. (c), Spiking preBötC neurons begin to synaptically activate other silent preBötC neurons, leading to aggregation of network activity via recurrent synaptic excitation, which is positive feedback. (d), the inspiratory burst occurs when recurrent synaptic activity is sufficiently strong to recruit postsynaptic inward currents such as I_{CAN} . Inspiratory bursts terminate due to intrinsic properties that remain unknown. Modified from: Feldman and Del Negro, *Nat Rev Neurosci* 7: 232–242, 2006.

undergo a recovery phase in which they gradually approach a baseline membrane potential largely determined by I_{K-Leak} and the by tonic inputs. The most excitable neurons spontaneously cross threshold and begin the next positive feedback cycle.

Given the diminishing evidence in support of the obligatory role of pacemaker properties in respiratory rhythm generation [8], a framework in which recurrent synaptic excitation evokes postsynaptic burst-generating membrane properties available to all pre-BötC inspiratory neurons, such as the group pacemaker hypothesis, is a viable mechanism that can explain key aspects of respiratory rhythmogenesis.

Acknowledgments

US National Science Foundation Integrative and Organismal Biology Award 0616099, The Suzann Wilson Matthews Faculty Research Award, and The Jeffress Memorial Trust.

References

1. Gray PA, Rekling JC, Bocchiaro CM, Feldman JL (1999) Modulation of respiratory frequency by peptidergic input to rhythmogenic neurons in the preBötzinger Complex. *Science* 286:1566–1568
2. Hayes JA, Del Negro CA (2007) Neurokinin receptor-expressing preBötzinger Complex neurons in neonatal mice studied in vitro. *J Neurophysiol* 97:4215–4224
3. Gray PA, Janczewski WA, Mellen N, McCrimmon DR, Feldman JL (2001) Normal breathing requires preBötzinger Complex neurokinin-1 receptor-expressing neurons. *Nat Neurosci* 4:927–930
4. Wang H, Stornetta RL, Rosin DL, Guyenet PG (2001) Neurokinin-1 receptor-immunoreactive neurons of the ventral respiratory group in the rat. *J Comp Neurol* 434:128–146
5. Guyenet PG, Sevigny CP, Weston MC, Stornetta RL (2002) Neurokinin-1 receptor-expressing cells of the ventral respiratory group are functionally heterogeneous and predominantly glutamatergic. *J Neurosci* 22:3806–3816
6. Smith JC, Ellenberger HH, Ballanyi K, Richter DW, Feldman JL (1991) Pre-Bötzinger Complex: A brainstem region that may generate respiratory rhythm in mammals. *Science* 254:726–729
7. Del Negro CA, Morgado-Valle C, Feldman JL (2002) Respiratory rhythm: an emergent network property? *Neuron* 34:821–830
8. Pace RW, Mackay DD, Feldman JL, Del Negro CA (2007) Role of persistent sodium current in mouse preBötzinger complex neurons and respiratory rhythm generation. *J Physiol* 580:485–496
9. Pena F, Parkis MA, Tryba AK, Ramirez JM (2004) Differential contribution of pacemaker properties to the generation of respiratory rhythms during normoxia and hypoxia. *Neuron* 43:105–117
10. Pace RW, Mackay DD, Feldman JL, Del Negro CA (2007) Inspiratory bursts in the preBötzinger complex depend on a calcium-activated nonspecific cationic current linked to glutamate receptors. *J Physiol* 582:113–125

Precentral Gyrus

Definition

The precentral gyrus is the cerebral gyrus immediately anterior and parallel to the central sulcus. It is part of the frontal lobe and is the primary motor cortex.

- [Primary Motor Cortex](#)
- [Gyrus precentralis](#)

Precerebellar Long-Lead Burst Neurons

CHARLES SCUDDER
Portland, OR, USA

Definition

Precerebellar neurons, in general, are neurons that have their somata in the brainstem or spinal cord and send their axons to the cerebellum. Precerebellar ► [long-lead burst neurons](#) (PCbLLBNs) (► [burst cells – long lead \(LLBNs\)](#)) are precerebellar neurons that have long-lead burst discharges during saccades. They comprise the major route for the transmission of saccadic commands to the cerebellum. All PCbLLBNs that have been identified to date have their somata in the pontine reticular formation or the pontine nuclei.

Characteristics Higher Order Processes

PCbLLBNs receive information from higher order saccadic command centers and relay this information to the ► [oculomotor vermis](#) and the ► [floccular lobe](#) of the cerebellum (see ► [Cerebellum – Role in Eye Movements](#)). Projections to the oculomotor vermis comprise the first leg of a trans-cerebellar route by which saccadic commands are processed in the cerebellum and then conveyed to the saccadic burst generator. At the burst generator, these processed commands are combined with a raw command conveyed directly from the same higher command centers, and are thought to provide the detail needed for generating accurate saccadic eye movements (see cerebellum – role in eye movements). PCbLLBNs provide the major, but not the only, input to the oculomotor vermis, and provide a minor input to the floccular lobe.

Command centers that provide the major input to PCbLLBNs are the deep and intermediate layers of

the ►superior colliculus, the ►frontal eye fields (FEF), the ►supplementary eye fields (SEF), and the ►lateral intraparietal area (LIP). The superior colliculus collects information from the above three cortical areas (FEF, SEF, LIP), the ►basal ganglia, the superficial layers of the superior colliculus, and other smaller projections, and is considered the final common path for the saccadic command.

Parts of the LLBN Pathway to the Cerebellum Groups of PCbLLBNs

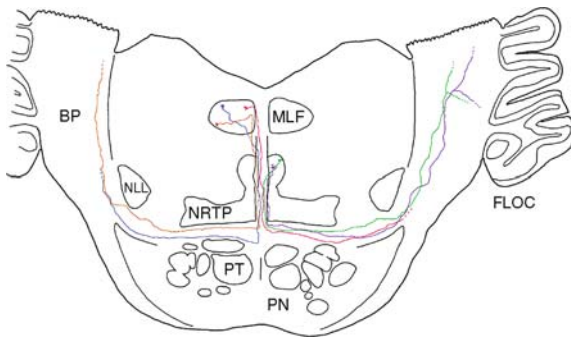
Somata of PCbLLBNs reside in four principal areas within the pons, and each area receives somewhat different information. By far the largest population is in the caudal ►nucleus reticularis tegmenti pontis (NRTP), both in the medial group of cells that extends dorsally from the main body of NRTP (Fig. 1), and to a lesser extent, in the medial part of the body of NRTP. The major input to this part of NRTP is from the superior colliculus, with a smaller input from the FEF and SEF. NRTP also receives a major feedback signal from the output of the midline cerebellum, namely, the fastigial nucleus.

A second group of PCbLLBNs resides in a diffuse collection of somata amid the fascicles of the medial

longitudinal fasciculus (the intrafascicular nucleus of the MLF, or IFN) just rostral to the abducens nucleus (Fig. 1). The third group resides in raphe pontis, which is located below the MLF immediately rostral to the abducens nucleus (not illustrated). The known inputs to these areas based on anatomical data arise from the superior colliculus and from the ►inhibitory burst neurons (IBNs) of the saccadic burst generator (see ►brainstem burst generator), but there may be other sources of input.

Locations of cell bodies and axonal projections for two of these three groups are illustrated in Fig. 1, which was derived from intraaxonally labeled neurons [1]. Axons of all NRTP, IFN, and raphe pontis PCbLLBNs course to the midline where they travel ventrally with other fiber bundles. Just above the pontine nuclei, they sharply turn either ipsilaterally or contralaterally and travel laterally in a well defined band of fibers between NRTP and the pontine nuclei. Subsequently, they enter the brachium pontis and travel dorsally to the cerebellum without ever branching in the brainstem. Several neurons originating in NRTP were observed to send collaterals to the floccular lobe, while none originating in the IFN or raphe pontis were so observed.

One group of investigators has found a fourth group of PCbLLBNs in the dorsolateral pontine nuclei [2]. The principal input to this group is from LIP, with a smaller input from the FEF. The dorsolateral pontine nuclei also receive heavy input from visual-motion sensitive cortical areas MST and MT, but PCbLLBNs presumably receive little of this input. This latter input goes mainly to neurons discharging during ►smooth pursuit eye movements, which are intermixed with PCbLLBNs in this region.



Precerebellar Long-Lead Burst Neurons.

Figure 1 Transverse section of the monkey brainstem at a level just rostral to the abducens nucleus is illustrated along with the somata and axons of five precerebellar LLBNs. Neurons were visualized using intraaxonal staining and were reconstructed using a camera lucida. Three somata are located in a fasciculated portion of the medial longitudinal fasciculus (MLF), and two others are located in a dorsomedial extension of nucleus reticularis tegmenti pontis (NRTP). Axons course to the midline and then ventrally to a lateral fiber tract just ventral to NRTP, where some cross and some do not (follow axon colors). Axons course laterally and then back dorsally in brachium pontis (BP). Staining faded before reaching the cerebellum (dotted lines). The NRTP neurons sent collaterals toward the floccular lobe (FLOC). NLL, nucleus of the lateral lemniscus; PN, pontine nuclei; PT, pyramidal tract.

Discharges of PCbLLBNs

Discharges of PCbLLBNs with somata in the reticular formation have been recorded extracellularly in medial NRTP, intra-axonally along their projection route, and extracellularly in the white matter of the oculomotor vermis and floccular lobe [1,3–5]. Like other LLBNs, they are mostly silent during fixations between saccades, but have a presaccadic firing that begins 21–300 ms before saccades in a preferred direction. Firing rate usually builds up towards a peak that usually also occurs before saccade onset. Firing ends near the time of saccade end.

PCbLLBNs in the reticular formation exhibit spatial properties that are intermediate between those of two common classes, namely ►directional and ►vectorial LLBNs. Like vectorial neurons, the range of directions for which a PCbLLBN may fire is less than a full hemifield, but it is usually larger than that of the superior-colliculus neurons that provide its major input. Unlike vectorial neurons, only a few PCbLLBNs

have closed ►movement fields. That is, the discharge rate and number of spikes of typical PCbLLBNs first increase as saccade size increases but then might plateau with further increases in size. A few act like directional neurons, in that discharge parameters continually increase as saccade size increases. For neurons that do not have vertical preferred directions, all have an ipsilateral component to their preferred direction and none have a ►contraversive component. PCbLLBN responses have also been shown to depend on the torsional component of the saccade, making movement fields three dimensional [6]. These spatial characteristics are probably produced by convergent input from appropriately selected superior-colliculus efferents.

In the dorsolateral pontine nuclei, LLBNs are one population within a range of burst neurons [2]. Discharges of some burst neurons lag saccade onset, and some burst neurons also exhibit responses during smooth pursuit eye movements. All possible preferred directions for bursts are present in the population.

Lower Level Processes

The major targets of PCbLLBNs originating in the NRTP, IFN, and raphe pontis are the “oculomotor vermis” (lobules VIc and VII) [7] and the ►fastigial oculomotor region (FOR; see cerebellum – role in eye movements). The fastigial nucleus is presumably innervated by collaterals of ►mossy fibers projecting to the vermis, but retrograde tracing data suggests that not all PCbLLBNs issue these collaterals [8,9]. PCbLLBN signals are used in the cerebellum to produce a burst in FOR neurons, whose timing and amplitude affect the duration and amplitude of the discharges of burst neurons in the saccadic burst generator. The cerebellum thus provides fine control of the size and direction of saccades (see brainstem burst generator).

Some PCbLLBNs with somata in NRTP project to the ►flocculus and paraflocculus as collaterals of axons projecting to the oculomotor vermis [1]. It is uncertain whether all LLBN input to the floccular lobe arises in this fashion. IFN and raphe pontis neurons also project to the floccular lobe, but these may be the burst-tonic neurons that are also found in these nuclei. There is no firm data about how PCbLLBN signals are used in the floccular lobe, but one possibility is that they are used to help remove saccade-related signals from the many inputs with mixed saccade and smooth eye-movement signals, leaving mainly the latter in the output pathway.

Pathology

There have only been preliminary studies using experimental lesions of NRTP at the location of PCbLLBNs. Temporary inactivation of caudal NRTP with lidocaine or muscimol in monkeys has produced

hypometric saccades, deficits in convergence and accommodation to a near target after a saccade, and aberrant torsional eye-position after a saccade [6,10]. Experimental lesions of the dorsolateral pontine nuclei produced deficits in smooth pursuit with no observable deficits in saccades. Specific lesions of raphe pontis have not been performed.

References

1. Scudder CA, Moschovakis AK, Karabelas AB, Highstein SM (1996) Anatomy and physiology of saccadic long-lead burst neurons recorded in the alert squirrel monkey. II. Pontine neurons. *J Neurophysiol* 76:353–370
2. Dicke PW, Barash S, Ilg UJ, Thier P (2004) Single-neuron evidence for a contribution of the dorsal pontine nuclei to both types of target-directed eye movements, saccades and smooth-pursuit. *Eur J Neurosci* 19:609–624
3. Crandall WF, Keller EL (1985) Visual and oculomotor signals in nucleus reticularis tegmenti pontis in alert monkey. *J Neurophysiol* 54:1326–1345
4. Kase M, Miller DC, Noda H (1980) Discharges of Purkinje cells and mossy fibers in the cerebellar vermis of the monkey during saccadic eye movements and fixations. *J Physiol (London)* 300:539–555
5. Ohtsuka K, Noda H (1992) Burst discharges of mossy fibers in the oculomotor vermis of macaque monkeys during saccadic eye movements. *Neurosci Res* 15:102–114
6. van Opstal AJ, Hepp K, Suzuki Y, Henn V (1996) Role of monkey nucleus reticularis tegmenti pontis in the stabilization of Listing's plane. *J Neurosci* 16:7284–7296
7. Thielert CD, Thier P (1993) Patterns of projections from the pontine nuclei and the nucleus reticularis tegmenti pontis to the posterior vermis in the rhesus monkey: A study using retrograde tracers. *J Comp Neurol* 337:113–126
8. Noda H, Sugita S, Ikeda Y (1990) Afferent and efferent connections of the oculomotor region of the fastigial nucleus in the Macaque monkey. *J Comp Neurol* 302:330–348
9. Yamada J, Noda H (1987) Afferent and efferent connections of the oculomotor cerebellar vermis in the macaque monkey. *J Comp Neurol* 265:224–241
10. Kaneko CRS, Fuchs AF (2004) Muscimol inactivation of the nucleus reticularis tegmenti pontis (nrtp) eliminates ipsilesional saccades. *Soc Neurosci Abs* 880.1

Precocial

Definition

Young born with hair or feathers, eyes open, the ability to move about immediately after birth and capable of leaving the nest within a few days.

►Neural Correlates of Imprinting

Precocious Puberty

Definition

The appearance of any sign of secondary sexual maturation, such as pubic hair, before the age of 8 years (or menarche before the age of 9 years) in girls and 9 years in boys.

► [Neuroendocrinology of Tumors](#)

An attribute is a feature, like being red, for which a linguistic predicate stands. Realists claim, while nominalists deny, that an attribute is a special entity (universal) that can be exemplified by several particular things.

► [Argument](#)

► [Logic](#)

Precuneus

Definition

Part of the parietal lobe visible in a median section. Has a virtually square shape (hence also called quadrate lobe). The precuneus appears to be implicated in complex, sensory evaluation processes, language processing as well as spatial and temporal orientation.

► [Telencephalon](#)

Prediction Error

Definition

A discrepancy between the expected and the experienced outcome of a behavioral situation. The prediction error is a relevant variable determining recruitment of dopaminergic action in the brain and formation of associations between events (stimuli and or behaviors).

► [Dopamine](#)

► [Neuroethological Aspects of Learning](#)

Precursor Cells

Definition

(Neural) precursor cells occur in both fetal and adult brains and are partially specialized; they undergo cell division and give rise to differentiated cells in a site-specific manner. In their normal states, adult precursor cells do not generate a wide variety of neurons. In the injured brain, adult precursor cells can partially replace neurons that are damaged or dead.

► [Adult Neurogenesis](#)

Predictive Eye Movements

Definition

Predictive eye movements occur whenever the motion of a target exhibits regular temporal features. Particularly with periodic movements, they compensate for the lag of the eye on the target implied by the reaction time, achieving either a nearly perfect synchronisation with the target (smooth pursuit of sinusoids at < 0.5 Hz) or even a lead (saccades tracking a target stepping back and forth at regular pace).

► [Oculomotor Control](#)

► [Saccade, Saccadic Eye Movement](#)

Predicate (Attribute)

Definition

A predicate is what can be said of something, truly or falsely. The linguistic predicate “is red” can truly be applied to red things. The relational predicate “is larger than” can be used to state a relation between two things.

Preferential Motor Reinnervation (PMR)

Definition

The bias and modest selectivity that motor axons exhibit in choosing motor endoneurial pathways and

end-organs over sensory pathways and end-organs during reinnervation.

►Peripheral Nerve Regeneration and Nerve Repair

Preferred Direction (of a Neuron)

Definition

Neurons that respond to motion of either discrete visual stimulus or of a structured background modulate the strength of their response as function of the direction of motion. Plots of the strength of the response, e.g., mean firing rate, against the angle of stimulus trajectory are called tuning curves. The angle corresponding to the peak of the curve defines the preferred direction of the neuron. Visuomotor neurons, such as tectoreticulospinal neurons (TRSNs) have a directional tuning for visual stimulus, as well as to the direction of orienting movement associated to motor components of their bursts. Preferred movement direction of a given neuron is determined from the tuning curves, in the same way as for visual or, more generally, sensory preferred directions.

►Reaching Movements

►SC-Tectoreticulospinal neurons (TRSNs)

in many of the cognitive and ►**executive control** functions necessary for goal directed behavior, including ►**working memory**, shifting of ►**selective attention**, decision-making and ►**response inhibition**. Disturbances in function are thought to contribute to the pathophysiology of several mental conditions, including ►**schizophrenia**, major ►**depression**, ►**post-traumatic stress disorder (PTSD)**, ►**attention deficit hyperactivity disorder (ADHD)** and susceptibility to ►**addiction**.

Characteristics

Anatomy

In common with all cortical areas, the PFC is a layered structure, with six layers in this case, and has the same major cellular constituents [1–5]. These include spiny ►**pyramidal neurons** with an excitatory glutamate phenotype whose axons ramify locally in addition to entering the white matter and projecting to other cortical and subcortical regions. The second major cell class consists of relatively aspiny, non-pyramidal ►**inter-neurons** whose inhibitory phenotype is GABAergic and whose axonal connections are strictly local. Several major subclasses of these local circuit neurons are distinguished by their content of calcium binding proteins or ►**neuroactive peptides** and by differences in their axonal targets, providing the necessary circuitry for feedback and feedforward inhibition within the cortex. Subsets of interneurons are also thought to entrain pyramidal cells to fire in ►**oscillations**, at frequencies deemed essential for specific forms of information processing [4].

In the past, cortical territories were defined by their inputs from specific nuclei of the ►**thalamus**, and this still constitutes a reasonable starting point for identifying cortical regions across species [3]. For the PFC, the principal thalamic division is the mediodorsal nucleus (MDTN). The MDTN is itself divided into three main subregions, each of which maintains reciprocal connections with portions of the PFC. (i) The paralamellar division is the most lateral part of the MDTN and innervates the cortical territory around the arcuate sulcus corresponding to Brodmann's area 8, also known as the ►**frontal eye fields**. This serves as the motor command region for voluntary (►**saccadic**) eye movements. (ii) Medial to the paralamellar division is the parvocellular region of the MDTN, which connects to the cortex along the dorsolateral convexity (DLPFC), including Brodmann's areas 9, 10 and 46, the latter lying within and along the banks of the principal sulcus. (iii) The most medial portion of the MDTN is the magnocellular division, which is interconnected to orbital regions of the cortex (named for their position above the eye socket) and to other ventral and medial surfaces of the frontal lobe, Brodmann's areas 11, 13, 14, 24, 25, 32 and 47/12. Collectively, these are termed the orbitomedial PFC (OMPFC). Areas 24, 25 and 32

Prefrontal Cortex

SUSAN R. SESACK

Departments of Neuroscience and Psychiatry,
University of Pittsburgh, Pittsburgh, PA, USA

Synonyms

Frontal cortex; Dorsolateral cortex; Orbitofrontal cortex

Definition

The prefrontal cortex was so named because it was discovered in electrical stimulation studies to be a "silent" region in front of the motor areas of the frontal lobe. It appears to have increased in size and complexity in the course of evolution, culminating in the human brain as approximately 30% of the cortical mantle and at least 11 different cytoarchitectonically defined areas according to Brodmann's nomenclature. It is involved

lie within the ►cingulate gyrus and so are also considered parts of the ►anterior cingulate cortex.

In addition to specific inputs from the MDTN, the PFC is also innervated by other thalamic nuclei within the anterior, ventral, medial and midline divisions as well as the pulvinar nucleus. As an association cortex, the PFC receives extensive inputs from other cortical regions organized in a hierarchical fashion [3]. Major afferents arise from other association areas, including those in the posterior parietal and inferior temporal regions. The sensory streams innervating the PFC appear to involve mainly visual, auditory and somatosensory projections to the DLPFC and primarily olfactory, gustatory and viscerosensory projections to the OMPFC. The OMPFC is also innervated by important structures within the ►limbic system, the ►hypothalamus, ►hippocampus and ►amygdala [1,3,5]. The amygdala is a quasi-cortical structure that regulates behavior by conditioned associations and its reciprocal connections with the PFC are important for facilitating appropriate emotional behaviors. It has been argued that within the OMPFC, orbital divisions are the main sites of sensory termination, whereas medial regions are the main origin of descending projections to autonomic regions [5]. Hence, these two subdivisions may function as viscerosensory and visceromotor regions, respectively.

The PFC, like most cortical structures, is extensively innervated by ►ascending neuromodulatory projection systems (see Essay of same name) arising in the brainstem and basal forebrain, including pathways conveying ►acetylcholine, ►dopamine, ►norepinephrine and ►serotonin inputs [3,6,7]. These projections provide essential modulation of cortical firing patterns and many studies demonstrate that either decreases or increases in critical levels of monoamines are sufficient to disrupt PFC function [6,7]. Conversely, pharmacological therapies for mental disorders (e.g., antipsychotic, antidepressant and anxiolytic medications) are often designed to alter monoamine transmission in an effort to restore more balanced activity in this region.

Many of the efferent projections of the PFC reciprocate the afferent inputs [1,3], including those to association cortices and to thalamic nuclei. Another major output of the PFC, as with many cortical regions, is to the ►basal ganglia. Cortical projections to the ►striatopallidum (see Essay of same name) are relayed back to the cortex via the thalamus, forming functional “loops” for the selection of appropriate actions and suppression of maladaptive responses. The DLPFC targets mainly the head of the ►caudate nucleus, forming a major associative loop that supports cognitive and executive functions, whereas the OMPFC projects to more ventral parts of the striatal complex, including the ►nucleus accumbens and participates in limbic circuitry for motivated behaviors. The brainstem

projections of the PFC include the ►superior colliculus for saccadic eye movement control and the pontine nucleus, which relays executive commands to the ►cerebellum for controlling the timing and coordination of movement and cognition. Interestingly, the OMPFC is the source of extensive projections to diencephalic and brainstem structures that are important regulators of autonomic output, including the amygdala, hypothalamus, ►periaqueductal gray, ►parabrachial nucleus and ►nucleus of the solitary tract [3,5]. Moreover, portions of the OMPFC are among the only cortical regions that project directly to brainstem monoamine neurons [3], placing this division of the PFC in a position to regulate the level of modulatory drive to the cortex generally. The latter connections are no doubt important for understanding the pathophysiology of mood disorders, in which brainstem monoamines are implicated in both cause and treatment.

On the basis of these differential inputs and outputs, the DLPFC is considered to be the main region within which spatial and object working memory and other executive functions are carried out [1–4,8]. The OMPFC has been deemed a viscerosensory and visceromotor network that guides behavior based on emotional experience [1,3,5,9]. Of course, the major subdivisions of the PFC are interconnected, so that goal directed behavior is accomplished by consideration of both external and internal perceptions [3].

Function

The PFC performs many essential cognitive functions whose complexity increases in the course of evolutionary development. The PFC guides behavior particularly when situations are novel or complex and is probably not involved in functions that are routine or well learned [1]. There is considerable consensus that the PFC is a major contributor to the processes underlying ►working memory, a short form of memory in which information is held temporarily in mind until it can be used to guide immediate behavior [1,2,4]. Such information is also available for mental manipulation and the PFC has sometimes been described as the brain’s “scratch pad.” The PFC provides a mechanism for bridging time between the near past and the actions that proceed from keeping this information “in mind.” In this way, the PFC is essential for preparing the motor systems for action and hence for future planning and logical sequences of action and thought [1].

Behavioral tasks in which a delay is interposed between cue and choice (►delayed-response tasks) are important tools for evaluating working memory performance in experimental animals and humans. Such tasks assess the ability to maintain a representation of spatial location, object identity or stimulus associations in the absence of the original cue and performance of these tasks is highly sensitive to PFC damage [1,2]. The

oculomotor variant of this test, the ►[delayed saccade task](#) was created to minimize movement in behaving animals and so to facilitate electrophysiological recording of neuronal activity during working memory. The resultant studies have depicted cells that respond to the presentation of the cue or to the go signal for the motor response. More importantly, many of these studies have described neurons that increase their activity during the delay period between the cue and the go signal. These “delay” cells appear to represent the maintenance of critical information obtained from the cue in order to guide future responding and so are widely considered as a neural correlate of working memory. Many studies report that delay period cells are spatially tuned, responding best to cues that dictate subsequent motor responses into specific regions of space [2]. The exact cellular mechanisms that underlie delay period activity are not yet known. Collateral synapses between pyramidal cells may form local reverberatory connections that could sustain such firing. Alternatively or in addition, delay period activity probably reflects long-range interconnections between the PFC and posterior association areas where similar firing patterns have been described [1,2,4,8]. Other electrophysiological recording studies, particularly those in the OMPFC, have described neurons that appear to encode the salience or reward value of stimuli, which is likely to subsequently influence motivation in motor responses [1].

Many of these observations from animal physiology have been verified to the extent possible in humans using variants of working memory or decision making tasks and functional imaging methods [1,8,9]. Functional magnetic resonance imaging (►[fMRI](#)) and positron emission tomography (►[PET](#)) monitor signals that reflect altered blood flow as indirect measures of activation in brain regions. Performance of tasks for which working memory is an essential component produce signals consistent with an increase in blood flow to the PFC. Moreover, many studies using this methodology have produced findings that extend theories regarding the cognitive functions of this region to include stimulus ►[encoding](#), sustained attention, decision making and motor preparation.

Disorders

Although lesions caused by stroke, tumor or accidental damage are rarely circumscribed within subdivisions of the PFC, some relatively distinct syndromes have been characterized [1]. Lesions that are centered in orbital regions of the OMPFC tend to cause loss of ►[response inhibition](#) [9], with changes in personality that include impulsiveness and recklessness. Patients have problems with selective attention and exhibit inappropriate decision making to the point of self-destructive and sociopathic behavior. Attentional problems are also seen with damage to medial portions of the OMPFC

that include the anterior cingulate cortex, in this case accompanied by affective blunting, apathy and withdrawal [1]. Lesions of the DLPFC produce a “dysexecutive syndrome” characterized by deficits in working memory and related cognitive functions, poor planning capability, difficulty in the execution of logically ordered sequences of behavior or language and attention deficits [1]. The consistent observation of attentional problems with damage to the PFC suggests that this cortical territory is important for regulating the attentional processes necessary for goal directed behavior [1]. Functional imaging studies of the anterior cingulate cortex in particular support a major role for this region in attentional mechanisms. Partly as a result of these observations, the PFC is considered a principal site of pathophysiology in ADHD [6].

There is ample evidence from functional imaging, postmortem and neuropsychological analyses for a significant malfunction of the PFC in ►[schizophrenia](#) [2,4]. Schizophrenic patients show deficits in working memory and other cognitive skills, consistent with reduced blood flow to the PFC during performance of tasks designed to test these functions. These and other “negative” symptoms form the core features of the illness; they are the most predictive of long-term prognosis and are the least susceptible to pharmacological intervention. Postmortem studies show structural alterations in both pyramidal and non-pyramidal neurons and reductions in markers of synaptic communication. Some of these deficits are specific to the PFC, while others are observed throughout the cortex. Most appear to be associated with the illness and not with treatment with antipsychotic medications [4].

Functional imaging and postmortem studies also report changes in the PFC in major ►[depressive disorders](#), including ►[bipolar depression](#) [5]. Altered metabolism/blood flow is particularly observed in the medial portions of the OMPFC and such changes are consistent with the symptom complex that accompanies lesions to this region. The earliest studies reported increased blood flow in the OMPFC with major depression, although later investigations have also shown decreased blood flow in this region. Some postmortem analyses have also reported reduced tissue volume in portions of the midline frontal cortex, primarily due to loss of glia and neuropil as opposed to a loss of neurons.

The PFC is highly susceptible to the impact of acute and chronic ►[stress](#) and it is well known that stress can exacerbate the symptoms of mental disorders [6,7,10]. Behavioral studies indicate that working memory performance is degraded in animals subjected to stress and several investigations report structural alterations in pyramidal neurons following exposure to chronically stressful conditions. Theories regarding the likely pathophysiology of PTSD often focus on the amygdala as a probable site of dysfunction, but these models also

suggest loss of inhibitory regulation of the amygdala by the OMPFC in this condition [10]. Stress is also a known contributor to recidivism in addiction disorders. Loss of inhibitory control of behavior by a weakened PFC system has been implicated in susceptibility to addiction and the impact of acutely stressful events on PFC activity may further destabilize individuals toward relapse [7].

References

1. Fuster JM (2001) The prefrontal cortex – an update: time is of the essence. *Neuron* 30:319–333
2. Goldman-Rakic PS (1999) The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. *Biol Psychiatry* 46:650–661
3. Groenewegen HJ, Uylings HBM (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog Brain Res* 126:3–28
4. Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* 6:312–324
5. Ongur D, Price JL (2000) The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 10:206–219
6. Arnsten AF, Li BM (2005) Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biol Psychiatry* 57:1377–1384
7. Moghaddam B (2002) Stress activation of glutamate neurotransmission in the prefrontal cortex: implications for dopamine-associated psychiatric disorders. *Biol Psychiatry* 51:775–787
8. Postle BR (2006) Working memory as an emergent property of the mind and brain. *Neuroscience* 139:23–38
9. Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 10:295–307
10. Rauch SL, Shin LM, Phelps EA (2006) Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research – past, present, and future. *Biol Psychiatry* 60:376–382

centers to peripheral organs. They are known as preganglionic neurons because their axons gather into small nerves that reach autonomic ganglia (sympathetic and parasympathetic) and terminate with innumerable nerve endings synapsing on ganglion neurons.

In the brain stem the main bilateral groups of preganglionic neurons are the accessory oculomotor nuclei of Edinger-Westphal projecting to the ciliary ganglia, the superior salivatory nuclei projecting to the pterygo-palatine and submandibular ganglia, the inferior salivatory nuclei projecting to the otic ganglia, the dorsal vagal nuclei projecting to ganglia in the trachea, oesophagus and gastro-intestinal tract, and part of the nucleus ambiguus projecting to cardiac ganglia.

In the spinal cord, autonomic neurons are grouped into bilateral columns in the ventral horn; the largest ones are part of the sympathetic pathways extending from the last cervical level (C8) to the second lumbar level (L2). Other columns, which are part of the parasympathetic pathways, occupy sacral levels (between S2 and S4). The preganglionic neurons, which are all cholinergic, receive two main inputs: from higher centers, for example the pontine micturition centre, the cardiovascular centers, several autonomic nuclei in the hypothalamus, and from the periphery via afferent (sensory) autonomic neurons, directly or through an interneuron.

- Ageing of Autonomic/Enteric Function
- Hypothalamus
- Parasympathetic Nervous System
- Parasympathetic Pathways
- Sympathetic Nervous System
- Sympathetic Pathways

P

Preganglionic Neuron

Definition

Within the autonomic nervous system – which is the set of central and peripheral nerve structures that control the activity of viscera (such as bladder, heart, intestines, trachea, glands) and of blood vessels – there are large arrays of neurons located in the spinal cord and the brain stem, arranged in columns and nuclei, that project their axons outside the central nervous system (CNS) and are part of the efferent (motor) pathways leading from brain

Preganglionic Neurotransmitters

Definition

Neurotransmitters released from preganglionic neurons to influence the activity of postganglionic neurons within autonomic ganglia. Acetylcholine is the primary neurotransmitter used by probably all preganglionic neurons. Co-transmitters in preganglionic neurons modulate the excitability of postganglionic neurons, or have presynaptic actions to affect further release of preganglionic neurotransmitters.

- Acetylcholine
- Autonomic Ganglia
- Preganglionic Neuron

Pregeniculate Nucleus (Primates)

- Intergeniculate Leaflet

Prehension

Definition

The act of taking hold, typically with the hand as in grasping.

- Coordination
- Motor Cortex – Hand Movements and Plasticity

Prejunctional

Definition

Prejunctional refers to the axon varicosity proximal to a neuroeffector junction, releasing neurotransmitters.

- Postganglionic Neurotransmitter

Prelude Neurons

- SC – Buildup Neurons

Premotor Areas

Definition

A term used to refer to secondary motor areas of cerebral cortex, particularly the dorsal and ventral areas on the lateral surface of the hemisphere. This term may also be used to refer to brain areas containing neurons that have synaptic linkages to motoneurons.

- Motor Cortex: Output Properties and Organization
- Visual Space Representation for Reaching

Premotor Cortex (Area 6)

Definition

The premotor cortex (area 6) appears to play a role in regulating grasping actions. In the caudal segments fibers arise from the pyramidal tract. Lesions frequently result in impaired grasping actions. Strength regulation of the grasping hand is likewise impaired.

- Telencephalon

Premotor Cortex (Area 8)

Definition

Frontal eye field. Plays an important role in voluntary control of eye movement. Lesions in this area cause loss of voluntary control of eye movement.

- Telencephalon

Premotor Interneurons

- Excitatory CPG Interneurons

Premotor Neurons

Definition

Neurons that have monosynaptic linkages to motoneurons.

Premotor Processing

Definition

Processing of information prior to generating movement that includes planning, anticipation of outcomes,

evaluation of rewards and decision making as to the best pattern of motor outputs to achieve particular goals.

- ▶ Visual Space Representation for Action
- ▶ Visual Space Representation for Reaching

Pre-mRNA

Definition

Transcribed RNA prior to the splicing process, containing both introns and exons.

- ▶ Alternative Splicing and Glial Maturation

Prenatal Brain Injury by Chronic Endotoxin Exposure

SANDRA REES

Department of Anatomy and Cell Biology,
University of Melbourne, Melbourne, Australia

Synonyms

Fetal brain injury; Brain inflammation

Definition

Many factors contribute to perinatal brain injury, with the major causes likely to be hypoxia-ischemia/reperfusion [1] and infection of the fetus and/or mother [2]. Clinical studies have indicated that there are significant associations between maternal infection, preterm birth, neonatal brain damage and increased levels of ▶ **proinflammatory cytokines** in the amniotic fluid and umbilical cord; the strength of specific correlations are still being deduced. Fetal inflammatory responses can occur in the absence of overt signs of infection or fetal compromise and it is possible that subclinical inflammation underlies otherwise unexplained brain injury. Preterm birth occurs in 7–10% of pregnancies; advances in perinatal care have led to a significant improvement in the survival of very premature (less than 30 weeks) and very low birth weight (less than 1,500 g) infants. However up to 10% of these infants develop spastic motor deficits and 20–50% suffer developmental and behavioral disabilities. The most common cerebral neuropathology observed in premature infants is white

matter injury, referred to as periventricular leukomalacia. This includes diffuse gliosis (▶ **microgliosis** and astrogliosis) extending throughout the white matter and also focal cystic infarction adjacent to the lateral ventricles in about 5% of cases. It is now increasingly recognized that the cerebral cortex and deep grey matter are also likely to be affected.

Invading microorganisms are thought to gain access to the amniotic cavity and fetus, most commonly, by ascending through the vagina and cervix [3]. This induces an innate immune response with inflammation of the chorioamniotic membranes and the production of proinflammatory cytokines. The cytokines and/or other inflammatory mediators then gain access to the fetus via swallowed amniotic fluid or fetal lungs, eyes or nasal membranes. It has been suggested that these agents increase the permeability of the blood–brain barrier with enhanced leucocyte infiltration of the brain mediated by brain chemokines; brain microglia and astrocytes will be stimulated to upregulate the production of cytokines and alterations to brain structures and/or overt injury will ensue depending on the severity of the inflammatory response.

Characteristics

Description of the Process

Lipopolysaccharide and the Inflammatory Response

In order to more fully understand the mechanisms involved in inflammatory-induced brain damage animal models are required with one of the specific goals being the development of therapeutic strategies. The bacterial endotoxin, lipopolysaccharide (LPS) is most commonly used to model the systemic inflammatory response induced by infection, although live bacteria have also been used. LPS is a major component of the outer membrane of gram negative bacteria. Since fetal inflammation associated with maternal infection is likely to be chronic in nature [3] models involving repeated exposure to LPS are most likely to mimic the human situation [4,5] although other models stand to contribute to an understanding of the inflammatory process. LPS has been administered to fetal rodents and sheep and neonatal rats, kittens and monkeys at a developmental age which equates to 25–30 weeks in the human fetus, a period of high vulnerability for white matter damage.

Cytokines

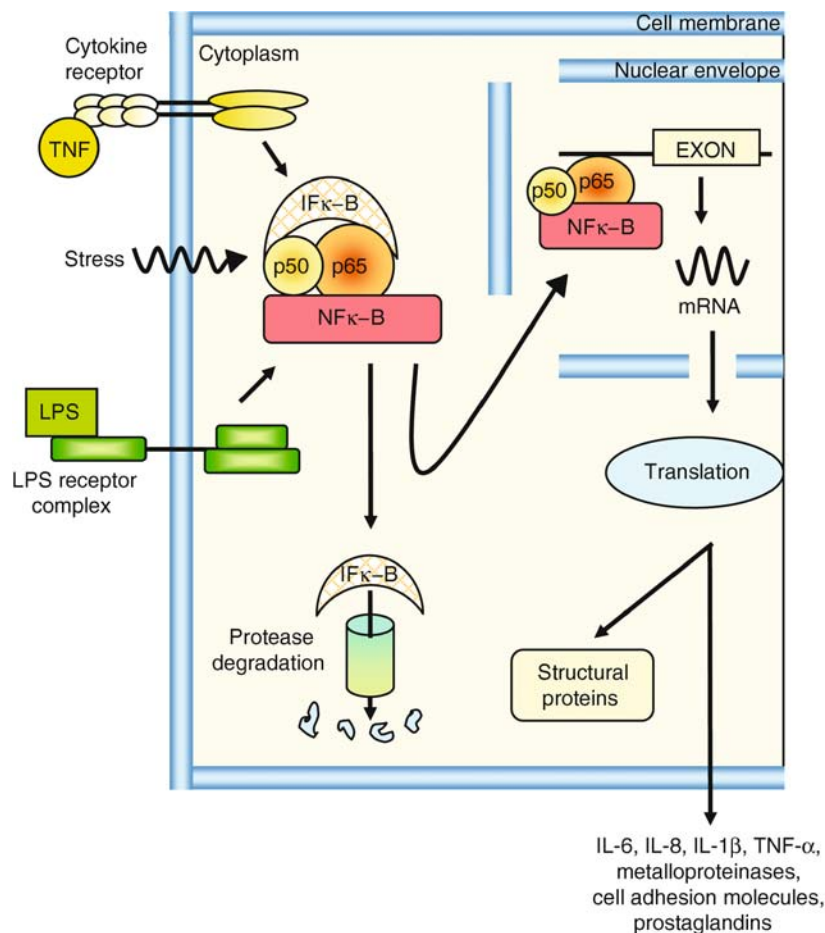
To contend with invading organisms, as typified by lipopolysaccharide, the innate immune response includes the generation of reactive oxygen species, phagocytosis and the production and release of cytokines and chemokines. LPS binds initially to LPS-binding protein (LBP), an acute phase protein released into the bloodstream from the liver [6]. LBP then appears to aid LPS in docking with the LPS receptor complex by forming a ternary complex with CD14 thus enabling LPS to be

presented to the LPS receptor complex consisting of Toll-like receptor-4 (TLR4) and MD-2 an extracellular adaptor protein, on the surface of myeloid and other cells. Binding to the complex activates transmembrane signaling pathways (Fig. 1) which result in the activation of the transcription factor nuclear factor (NF)- κ B, containing subunits p50 and p65 as homo- or heterodimers. NF- κ B binding activity can be induced by changes in the intracellular redox status and LPS is known to be one of the most potent activators of this pathway. NF- κ B is normally present in the cell cytoplasm forming an inactive complex with an inhibitor I- κ B α . Following cellular activation, I- κ B α is phosphorylated by I- κ B kinase; its subsequent degradation by cytoplasmic proteases releases NF- κ B which is translocated to the nucleus where it regulates transcription of several genes including cell adhesion

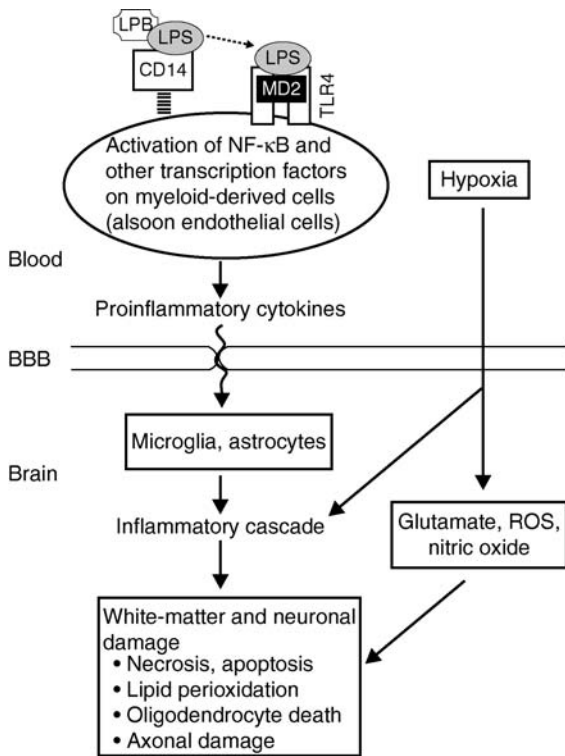
molecules, metalloproteinases and the pro-inflammatory cytokines, IL-1 β , IL-6 and TNF- α . For example TNF- α is elevated within 2 h of LPS exposure in the preterm ovine fetus (Fig. 2).

Blood-Brain Barrier

Systemic cytokines (and LPS) can then bind to receptors on cerebral endothelial cells or periventricular cells initiating downstream signaling events which include an increase in prostaglandin synthesis and altered cGMP and nitric oxide levels. This results in increased blood-brain barrier (BBB) permeability for at least 24 h after LPS exposure particularly in white matter tracts; the exact molecular site within the blood vessels at which the leak to proteins occurs is not yet clear. Cytokines and proinflammatory substances can then pass into the brain activating microglia and



Prenatal Brain Injury by Chronic Endotoxin Exposure. Figure 1 In response to proinflammatory cytokines, endotoxins or environmental stress, the nuclear factor (NF)- κ B pathway is activated. NF- κ B (containing subunits p50 and p 65) is normally present in the cytoplasm forming an inactive complex with inhibitory factor (IF- κ B). Following cellular activation, IF- κ B is phosphorylated and subsequently degraded by cytoplasmic proteases. This releases NF- κ B which is translocated to the nucleus where it regulates the transcription of several genes including proinflammatory cytokines.

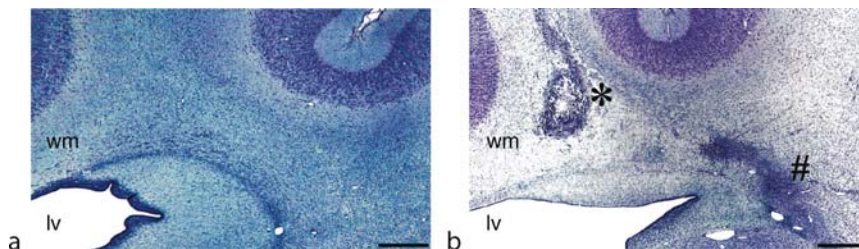


Prenatal Brain Injury by Chronic Endotoxin Exposure. Figure 2 Possible activation of the inflammatory cascade by endotoxin (lipopolysaccharide, LPS). LPS binds to LPS binding protein (LBP) which then forms a ternary complex with CD14, enabling LPS to be presented to the LPS receptor complex consisting of Toll-like receptor 4 (TLR4) and MD-2. This activates NF- κ B and other signaling pathways. Proinflammatory and other proteins are transcribed; they affect the permeability of the blood–brain barrier, perhaps via the up-regulation of prostaglandins, and allow the entry of proinflammatory substances and circulating leukocytes into the brain. Here there is activation of microglia and astrocytes to up-regulate cytokine production; this ultimately leads to white-matter and neuronal damage. If hypoxia is also involved, excess extracellular glutamate will result in further nitrosative and oxidative stress, exacerbating neuronal and axonal damage.

astrocytes to release cytokines, oxygen free radicals and other factors which will have multiple effects on the brain ranging from altered neuronal development to overt injury (Fig. 3). A recent microarray study in the LPS-exposed neonatal rat demonstrated altered gene expression of hundreds of inflammatory molecules and also cell-death associated molecules in the brain. In the adult brain, TLR4 receptors are found in regions devoid of the BBB namely the circumventricular organs (CVOs) and also the choroid plexus, meninges and scattered cells within the brain parenchyma. It has been postulated that LPS binds to TLR4 in the CVOs inducing an inflammatory reaction which is then disseminated throughout the brain. In the neonatal brain mRNA for CD14 receptors has been identified although their cellular distribution is not known.

Oxidative and Nitrosative Stress

Reactive oxygen species (ROS) are toxic oxygen metabolites produced in small quantities during the normal cellular metabolic processes in mitochondria via univalent reduction of molecular oxygen. In response to stimuli, including an imbalance in the cellular redox status, the formation of ROS increases dramatically. ROS interact with the lipid components of cell membranes, initiating lipid peroxidation resulting in the breakdown of lipid constituents into highly reactive by-products including lipid aldehydes, for example 4-hydroxynonenal (4-HNE). These reactive aldehydes then bind to and modify protein creating protein adducts. In addition to oxidative stress, nitrosative stress results from nitric oxide (NO) released from reactive microglia reacting with superoxide anions to form peroxynitrite which targets tyrosine residues of proteins to form nitrotyrosine residues. Both of these processes are highly damaging to cell membranes. Lipid peroxidation of membranes can occur in the cerebral hemispheres within 6 h of LPS exposure in the ovine fetus [7]. The major antioxidant defence system that prevents the intracellular accumulation of ROS is the glutathione system. Reduced glutathione (GSH) acts as both a free radical scavenger and as a substrate in the GSH redox cycle. During late



Prenatal Brain Injury by Chronic Endotoxin Exposure. Figure 3 Section of the cerebral hemispheres from control (a) and LPS-exposed (b) fetal sheep at 70% of gestation (term ~147 days). Repeat bolus doses of LPS resulted in both focal (*) and diffuse (#) white matter (wm) injury; lv – lateral ventricle. Image courtesy of Dr Jhodie Duncan. Scale = 528 μ m.

gestation, there are marked increases in the antioxidant protective capacity. The combination of an immature defence system, LPS challenge and localized oxidative and nitrosative stress exposes the fetal brain to a high risk of ROS-mediated tissue injury.

Glial Response

Within the preterm ovine and rat brain activation of microglia is the most prominent glial response after LPS exposure; there is a significant correlation between the intensity of microglial/macrophage invasion and the extent of white matter injury indicating a substantial role for microglial activation in the manifestation of and/or response to injury [4,5]. Currently it is not certain whether these cells are mainly microglia already resident in the brain or macrophages invading from the circulation. Of interest is the recent suggestion that the high density of activated microglia in the white matter during normal fetal human brain development might potentially prime this area for diverse brain insults characterized by the activation of microglia; this also appears to be the case in the ovine and rodent fetus.

Axonal Injury

This could occur as a result of increased glutamate levels in the extracellular space induced by cytokine activation of glutamate-containing astrocytes and the subsequent activation of glutamate receptors on oligodendrocytes or the myelin sheath itself causing a toxic influx of Ca^{2+} . Excess Ca^{2+} will likely cause disruption to mitochondrial function and damage to the structural integrity of the axon. During the peak gestational age for white matter damage, developing oligodendrocytes (preoligodendrocytes) predominate [8]. The basis for this maturational susceptibility could be related to preferential vulnerability to free radicals, cytokines, glutamate toxicity or a mismatch of antioxidant enzymes and a subsequent imbalance of oxidative metabolism.

NF- κ B Activation in the Brain

Within the brain the role of NF- κ B in neuronal survival is controversial with studies supporting both a neurodestructive or neuroprotective role, the latter possibly by upregulation of anti-apoptotic genes [9]. Perhaps this dichotomy is due to differences in stages of neuronal development, different monomeric composition, degrees of NF- κ B activation or different combinations of cellular stimuli. It has been suggested that activation of NF- κ B in neurons might protect them against degeneration whereas activation in microglia promotes neuronal degeneration via cytokine production [9]. Chronic systemic administration of LPS in the ovine fetus leads to increased binding activity of NF- κ B subunits in specific regions of the fetal brain and

placenta within 6 h of exposure [7]. There was no clear-cut relationship however between alterations in levels of NF- κ B and the vulnerability to endotoxic damage. In the cerebral hemispheres where damage occurs NF- κ B was not upregulated whereas in the hippocampus where damage does not occur NF- κ B was elevated. Clearly the activation of NF- κ B can result in several downstream signaling pathways and an upregulation does not necessarily signal that brain damage will ensue. Therefore blocking NF- κ B transcription might not be a means of protecting against brain injury.

Higher Level Processes

Cerebral white matter injury resulting from ►chronic endotoxin exposure in the prenatal brain (►prenatal brain injury (PBI)) is likely to have consequences on the overlying cortex; the cell bodies associated with damaged cortical efferent axons are likely to die. Cortical neurons in layers 5 and 6 demonstrate an upregulation of beta amyloid precursor protein (a marker of cellular stress) after chronic LPS exposure not only in regions of overt white matter damage as might be expected, but also in adjacent gyri. This suggests that chronic endotoxin exposure also induces damage to cortical neurons either directly or secondarily to sensory deafferentation. Progressive post-injury reorganization of the undamaged cerebral cortex will play a role in the underlying mechanisms of ensuing neurological sequelae. It is becoming increasingly recognized in human MRI studies of premature infants that subtle alterations in cerebral structure are common, particularly in the extremely immature infant. Effects of LPS on other aspects of development such as neurogenesis remains to be elucidated.

Interaction Between Inflammation and Hypoxemia

Elucidating the mechanisms involved in inflammatory-induced brain injury is made more complex by the observation that inflammation can interrupt hemodynamic stability and that activation of inflammatory pathways is involved in the neural responses to hypoxia/ischemia. In animal models the inflammatory cascade and associated brain damage appears to be exacerbated if cerebral oxygen delivery is also reduced. LPS administered in repeat bolus doses at 70% of gestation results in fetal hypoxemia, hypotension, acidemia and associated brain damage in the ovine fetus [4]. A chronic infusion of the same or higher total dose of LPS does not result in significant alterations in fetal physiology but does cause brain injury, which is not as severe as when accompanied by hypoxemia [5]. Furthermore, endotoxin has been shown to sensitize the immature brain to hypoxic-ischemic injury [10]. In human pregnancies where intrauterine inflammation is accompanied by fetal asphyxia, there appears to be a significant increase in the risk of cerebral palsy.

Thus there are likely to be synergistic pathways between hypoxia and infection/inflammation which potentiate the evolution of brain damage although it is evident that inflammation alone can indeed cause fetal brain injury. It is possible that infection could impair oxygen delivery to the fetal brain via effects on gas exchange in the placenta. Histologic chorioamnionitis when compounded with a placental perfusion defect has been shown to enhance the risk of abnormal neurologic outcome in extremely low birth weight infants.

Function

It is likely that altered brain structure and white matter lesions resulting from ►[brain inflammation](#) will have long term consequences for brain development and function, including cognition, behavioral and motor abilities. Inflammation might also have long term effects on autonomic and neuroendocrine responses, including the manifestation of fever. It has recently been shown that neonatal exposure to LPS attenuates the febrile and CNS neurochemical responses to an LPS challenge in later life; this might equate to an altered ability to combat diseases after birth.

References

1. Volpe JJ (2001) Perinatal brain injury: from pathogenesis to neuroprotection. *Ment Retard Dev Disabil Res Rev* 7(1):56–64
2. Dammann O, Leviton A (1997) Maternal intrauterine infection, cytokines and brain damage in the preterm newborn. *Pediatrics Res* 42:1–8
3. Romero R, Chaiworapongsa T et al. (2003) Micronutrients and intrauterine infection, preterm birth and the fetal inflammatory response syndrome. *J Nutr* 133 (5 Suppl 2):1668S–1673S
4. Duncan JR, Cock ML et al. (2002) White matter injury after repeated endotoxin exposure in the preterm ovine fetus. *Pediatric Res* 52:1–9
5. Duncan JR, Cock ML et al. (2006) Chronic endotoxin exposure causes brain injury in the ovine fetus in the absence of hypoxemia. *J Soc Gynecol Invest* 2006 (13):87–96
6. Palsson-McDermott EM, O'Neill LA (2004) Signal transduction by the lipopolysaccharide receptor, Toll-like receptor-4. *Immunology* 113:153–162
7. Briscoe TA, Duncan JR et al. (2006) Activation of NF-κB transcription factor in the preterm ovine brain and placenta after acute LPS exposure. *J Neurosci Res* 83:567–574
8. Back SA, Han BH et al. (2002) Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. *J Neurosci* 22(2):455–463
9. Mattson MP, Camandola S (2001) NF-κB in neuronal plasticity and neurodegenerative disorders. *J Clin Invest* 107(3):247–254
10. Eklind S, Mallard C et al. (2001) Bacterial endotoxin sensitizes the immature brain to hypoxic-ischaemic injury. *Eur J Neurosci* 13(6):1101–1106

Prenatal Brain Injury (PBI)

Definition

It involves fetal brain injury and inflammation.

► [Prenatal Brain Injury by Chronic Endotoxin Exposure](#)

Preoptic Area

Synonyms

► [Area preoptica](#)

Definition

Situated at the lateral wall of the third ventricle, close to the optic recess. The region comprises three nuclear areas: periventricular nucleus, medial preoptic nucleus and lateral preoptic nucleus.

The area is also in the direct vicinity of the organum vasculosum of the lamina terminalis and plays a role in thermoregulation, hypovolemic thirst, male sexual behavior, brood care, gonadotropin secretion and locomotion.

► [Diencephalon](#)
 ► [Hypothalamus](#)
 ► [Nocturnal/Diurnal](#)

Preparatory Postural Adjustments

► [Anticipatory Postural Responses](#)

Prepositus Hypoglossal Nucleus

Synonyms

► [Nucl. prepositus hypoglossi](#)

Definition

The rod-shaped nucleus rostral to the hypoglossal nerve in the oculomotor control center which plays an important role in tracking moving objects – with the eyes, coordination of fast eye movements and fixation on objects. The nucleus has afferents from the

cerebellum, vestibular „ nuclei as well as the interstitial nucleus (Caj al). Efferents to the nuclei of the eye muscles.

► Myelencephalon

Prepulse Inhibition

Definition

A decrease of the response to a startle inducing stimulus, when the stimulus is preceded by a weak stimulus that does not induce a startle response.

► Startle Response

Prepyriform Cortex

► Olfactory Cortex

Pressure Ejection

Definition

► Microiontophoresis and Micropressure Ejection

Pressure Micro-ejection

► Microiontophoresis and Micropressure Ejection

Pressure Receptors

► Cutaneous Mechanoreceptors, Anatomical Characteristics

Presynaptic Inhibition

JORGE N. QUEVEDO

Department of Physiology, Biophysics and Neuroscience, Centro de Investigación y de Estudios Avanzados del I.P.N, Mexico City, Mexico

Synonyms

Decrease of synaptic effectiveness

Definition

Presynaptic inhibition (PSI) refers to a decrease of transmitter release at central synapses. Five decades ago, it was reported that activation of afferent fibers originating in flexors led to depression of monosynaptic group Ia ►excitatory postsynaptic potentials (EPSPs) evoked on extensor motoneurons in the cat spinal cord [1]. This depression occurred with no detectable changes in the time course of monosynaptic EPSPs, membrane potential or motoneurone excitability [1,2]. It is now known that PSI occurs broadly within the central nervous system of both vertebrates and invertebrates, and that synaptic efficacy at axon terminals from sensory afferents, descending systems or interneurons [3] can be subject to an inhibitory control by a number of neurotransmitters and presynaptic receptors [4].

Characteristics

PSI Associated with Primary Afferent Depolarization (PAD)

PAD as a Measure of PSI in the Spinal Cord

Stimulation of sensory nerves produces a slow negative potential recorded in dorsal roots via depolarization of intraspinal terminals of afferent fibers. This depolarization, termed ►primary afferent depolarization (PAD), is electrotonically propagated to the dorsal roots and can be recorded as a ►dorsal root potential (DRP). It can also be recorded intra-axonally in the dorsal horn. When the intra-axonal membrane potential produced by PAD reaches firing threshold, back-propagating action potentials are seen, and are called ►dorsal root reflexes (DRRs). Owing to the parallel time course of PSI and PAD, it has been assumed that PAD is responsible for PSI and that both phenomena are mediated by the same mechanisms [2,3].

Mechanisms Involved in the Generation of PAD

Pharmacological and electrophysiological studies have lead to the conclusion that PAD is primarily mediated by last-order GABAergic interneurons, and generated by the activation of presynaptic ionotropic GABA_A receptors [2,3]. GABA_A receptors are Cl⁻-permeable, and their activation drives the membrane potential towards the Cl⁻ reversal potential. Because a Na⁺, K⁺, 2-Cl⁻ cotransporter (NKCC1) maintains the Cl⁻ reversal

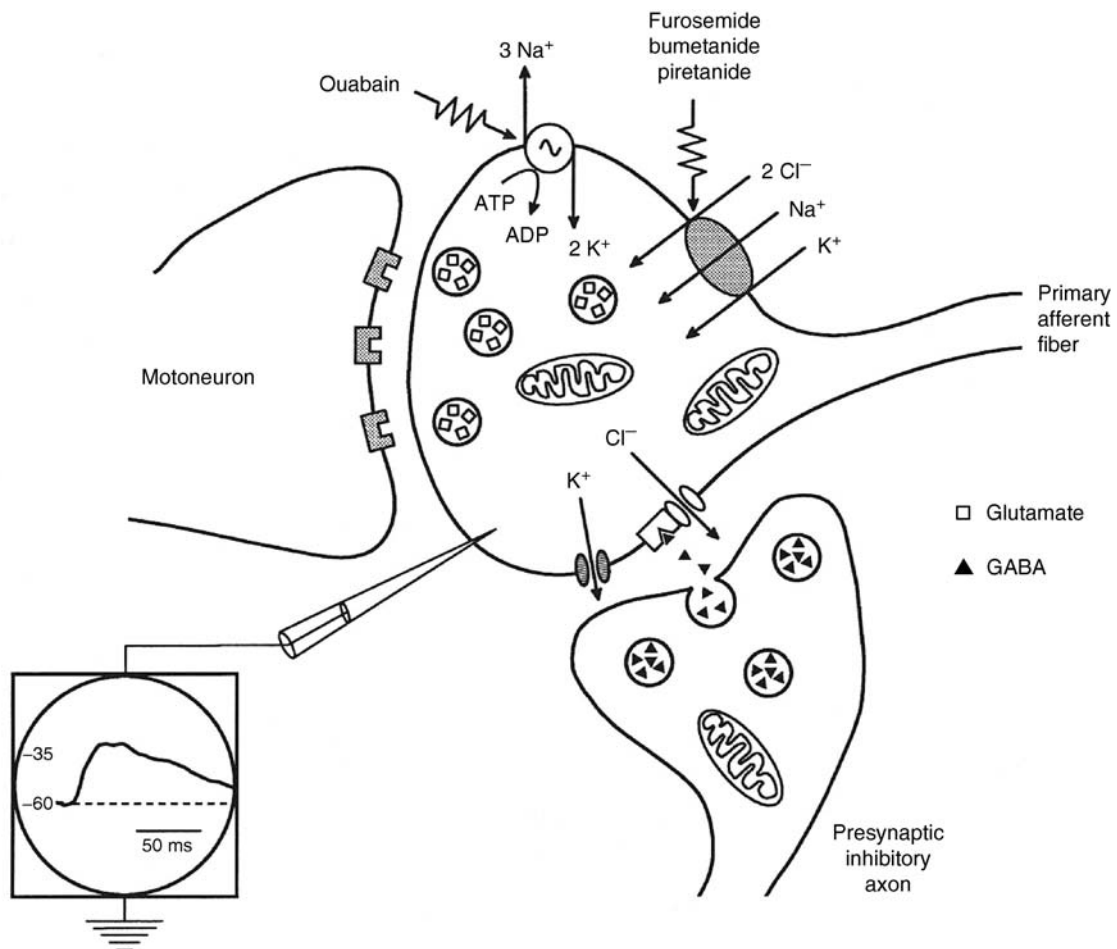
potential less negative than the membrane potential, GABA_A receptor activation leads to an efflux of Cl⁻ ions and consequent depolarization of afferent terminals, i.e. PAD (Fig. 1) [4]. The increase in Cl⁻ conductance reduces transmitter release by inactivation of voltage-gated Na⁺ and Ca²⁺ channels, or by shunting the membrane current to prevent spike invasion into the axon terminals [3]. The depolarization produced by activation of GABA_A receptors can also enhance spontaneous transmitter release in the dorsal horn neurons by activating voltage-gated Ca²⁺ channels [5].

Interneurons Mediating PAD

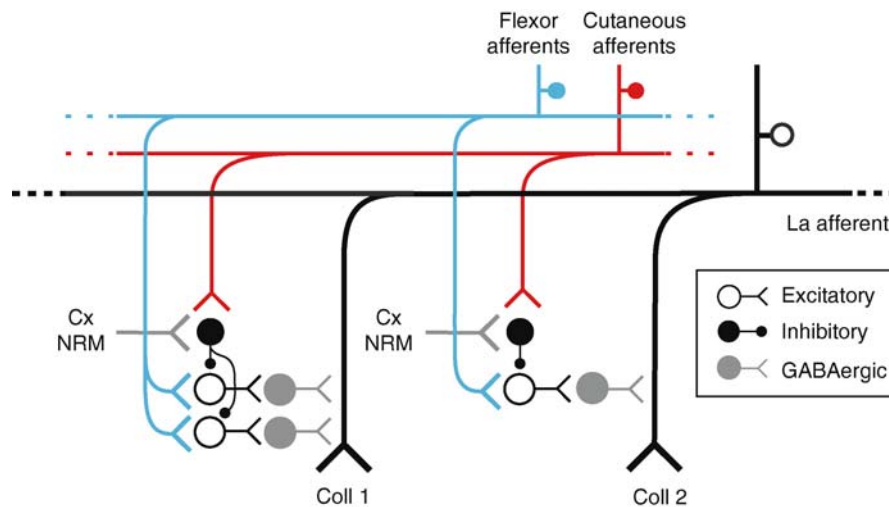
There is clear anatomical evidence for the existence of GABAergic axo-axonic synapses on ►muscle spindle group Ia and II, muscle ►Golgi tendon organ group Ib,

and large diameter cutaneous afferents. However, a direct identification of interneurons mediating PAD is still lacking [3]. In addition to activation of conventional interneuronal circuits, PAD on myelinated and unmyelinated cutaneous afferents may be also accounted for by non-spiking microcircuits that involve dendroaxonic GABAergic contacts or GABA spill-over [6].

The shortest pathway mediating PAD of group I, group II and large diameter cutaneous afferents fibers is thought to be trisynaptic (Fig. 2), including first order excitatory and last-order GABAergic interneurons interposed [2,3]. The long duration of PAD (Fig. 1), suggests that last-order interneurons mediating PAD produce a prolonged burst of spikes following a brief afferent input. However, since a single interneurone spike is able to generate a similarly long-lasting DRP,



Presynaptic Inhibition. Figure 1 Schematic representation of a presynaptic inhibitory axon from a GABAergic interneurone contacting a primary afferent fiber. The activation of GABA_A receptors present on afferent terminals drives the membrane potential towards the Cl⁻ reversal potential. Because a Na⁺, K⁺, 2-Cl⁻ cotransporter maintains the Cl⁻ reversal potential less negative than the membrane potential, GABA_A receptor activation leads to an efflux of Cl⁻ ions and consequent depolarization of afferent terminals (i.e. PAD). This depolarization could be recorded theoretically by a microelectrode inserted in the terminal of the primary afferent. Na⁺ concentration inside the terminal is regulated by the Na⁺-K⁺-ATPase pump. Several drugs that can inhibit the cotransporter are indicated. (From [4]).



Presynaptic Inhibition. Figure 2 Schematic diagram illustrating the local character of primary afferent depolarization (PAD) in collaterals of a single muscle spindle (Ia) afferent (black lines) ending at two different spinal levels. PAD produced by stimulation of flexor afferents (blue lines) is mediated by at least two interneurons interposed. First-order and last-order interneurons are excitatory (open circles) and GABAergic (gray circles), respectively. PAD evoked in collateral 1 (Coll 1) and collateral 2 (Coll 2) is mediated by separate sets and number of interneurons. PAD evoked by stimulation of flexor afferents in each collateral is reduced by stimulation of cutaneous (red lines), and the corticospinal (Cx) and raphespinal (NRM) (gray lines) systems via different sets of inhibitory interneurons (black circles). From [7].

PAD may be due to slow kinetics of GABA release, action, or uptake [3].

Interneurons mediating PAD are spatially segregated in the spinal cord, generally located in regions corresponding to the termination sites of the various afferent modalities. PAD of cutaneous and group I muscle afferent fibers is mediated by interneurons located in the middle and lateral parts of Rexed laminae III-IV, and medial Rexed laminae V-VI, respectively. PAD of group II afferents is produced by separated sets of interneurons into dorsal horn and intermediate zone, and the PAD of group II afferents seen in mid-lumbar and sacral spinal segments is also mediated by distinct populations of interneurons [3,8].

Organization of Pathways Mediating PAD

The patterns of PAD evoked by stimulation of sensory and supraspinal inputs differ for each afferent modality, suggesting that interneuronal pathways mediating PAD are modulated in a rather selective and complex manner. However, a primary mechanism of recruitment of PAD appears associated with a negative feedback control of their activated afferents.

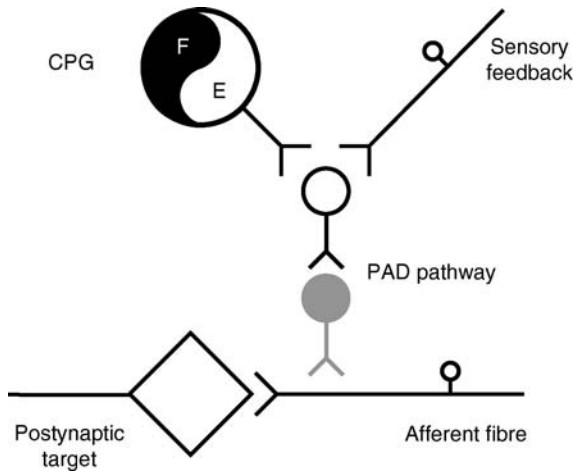
Muscle Afferents

PAD of Ia afferents is most effectively produced by stimulation of group Ia and group Ib flexor afferents, and vestibulospinal inputs; it is also inhibited by stimulation of various supraspinal (corticospinal, rubrospinal, reticulospinal and raphespinal serotonergic systems) and

peripheral systems (large cutaneous and joint afferents) (Fig. 2). PAD of group Ib afferents occurs predominantly following activation of group Ib afferents from flexors and extensors, joint, and large cutaneous afferents (but may also be inhibited by these cutaneous afferents). In contrast to PAD of group Ia afferents, PAD of group Ib afferents is evoked by corticospinal, reticulospinal and raphespinal serotonergic systems, and also by the noradrenergic nucleus locus coeruleus, cerebellum and the vestibulospinal tract [3].

The different patterns of PAD of group Ia and group Ib afferent fibers produced by segmental and supraspinal inputs suggest that PAD is mediated by different sets of last-order GABAergic interneurons. Yet PAD of group I muscle afferents can be modulated differentially in afferent fibers ending at two separate spinal levels, or even in proximal collaterals of the same afferent fiber (Fig. 3). This local character of PAD is likely due to the activation of different sets of interneurons mediating PAD [3,7].

PAD of group II afferents is generally evoked by stimulation of group II, cutaneous, joint and pudendal afferents, as well as by the noradrenergic locus coeruleus and serotonergic raphespinal systems. It is most effectively evoked by group II afferents ending at the same spinal sacral or midlumbar segment. This implies that separate populations of interneurons mediate PAD of group II afferents projecting to these segments. PAD of group II afferents is generally stronger than PAD of group I afferents, indicating that PAD of group I and group II afferents is mediated by different sets of interneurons [3,8].



Presynaptic Inhibition. Figure 3 Diagram of systems modulating presynaptic inhibitory pathways during locomotion. Synaptic transmission from afferent fibers to postsynaptic targets (open diamond) is modulated by PAD-related PSI mechanisms. Inputs from the locomotor pattern generator (CPG) circuitry and the sensory feedback from limbs in movement modulate PAD pathways, which are mediated by first-order excitatory (open circles) and last-order GABAergic (gray circles) interneurons. PAD-related PSI mechanisms participate in shaping motor pattern activity to adapt movement limbs to the environment. Adapted from [9].

Cutaneous Afferents

PAD of low threshold cutaneous afferents is produced by stimulation of low threshold cutaneous, group Ib, group II, and high threshold muscle afferents, as well as by stimulation of corticospinal, reticulospinal, rubrospinal and the raphespinal serotonergic system. PAD of low threshold cutaneous afferents is larger in response to activation of their specific afferent modality (e.g. rapidly-adapting vs. slowly adapting). Therefore, PAD of low threshold cutaneous afferents plays an important role in sensory discrimination by enhancing contrast and eliminating surplus excitation. High threshold cutaneous afferents (A δ and C) are more effectively depolarized by noxious stimulation, as well as by stimulation of reticulospinal and raphespinal serotonergic systems [3]. However, because of the scarcity of axo-axonic GABAergic contacts on A δ and C fibers, spillover mechanisms may be involved in the generation of PAD in these fibers [3,6].

PAD Evoked by Non-GABAergic Mechanisms

The accumulation of K⁺ ions in the extracellular space following activation of spinal interneurons was proposed as a mechanism to explain PAD. However, changes in extracellular K⁺ cannot account for all of the characteristics of PAD associated with stimulation of peripheral nerves or supraspinal pathways [3].

In addition to GABA_A receptors, primary afferents contain a diversity of receptors whose activation can evoke depolarization of terminals and in consequence PSI. Stimulation of high threshold afferent fibers evokes DRPs including a large component evoked by activation of NMDA and AMPA/kainate ionotropic glutamate receptors [6]. Activation of presynaptic AMPA and kainate receptors depresses excitatory transmission in dorsal horn neurons, but increases spontaneous transmitter release, both kinds of effects being apparently produced by PAD [5]. Capsaicin depresses excitatory synaptic transmission evoked by stimulation of C afferent fibers and this depression is also related to PAD [5].

The spinal cord receives diffuse projections from several descending monoaminergic nuclei that modulate PAD pathways. For instance, stimulation of the serotonergic nucleus raphe magnus produces PAD on group Ib afferent fibers [3]. However, because iontophoretic application of serotonin and noradrenaline produces no change in the intraspinal threshold of group I afferents, it is unlikely that PAD occurs by a direct effect of these monoamines on afferent fibers [3].

Stimulation of the noradrenergic locus coeruleus and the serotonergic raphe nucleus produces PAD on group II afferent fibers associated with a concomitant depression of synaptic transmission of the same afferents, suggesting participation of a presynaptic inhibitory mechanism. Nevertheless, the decrease in transmitter release appears not to be mediated by direct actions of monoamines on group II afferents, but indirectly via modulation of the interneuronal pathways mediating PAD [3,8].

Localization of serotonin and noradrenaline receptor subtypes is apparently restricted to high threshold cutaneous afferents [3,8]. Indeed, A δ and C fibers are depolarized by direct application of serotonin, yet there is no clear association between PAD and decrease in synaptic effectiveness of these afferents [3].

PSI not Associated with PAD

While PAD is generated predominantly by the activation of GABA_A receptors, it is well known that activation of presynaptic G-protein coupled receptors, such as GABA_B, can lead to PSI. This type of PSI is linked to intracellular signaling pathways that inhibit voltage-gated Ca²⁺ channels, with no associated presynaptic depolarization. Moreover, in contrast to the activation of GABA_A receptors, activation of GABA_B receptors produces a longer-lasting component of inhibition of the monosynaptic EPSPs [3].

Activation of metabotropic adenosine and cannabinoid receptors also inhibits transmitter release by inhibition of voltage-gated Ca²⁺ channels coupled to G-protein receptors [5]. The inhibitory effects of monoamines on the synaptic efficacy of high threshold cutaneous afferents may be also produced by activation

of metabotropic receptor subtypes coupled to signal transduction pathways [3,8].

A long-lasting inhibition of the monosynaptic reflex has been associated with a ►**homosynaptic depression** of the synapse between group Ia afferents and motoneurons. This depression also occurs in the absence of changes in motoneurone excitability and results from postactivation transmitter depletion [3].

PSI and Function

PSI pathways are modulated during real and fictive motor behaviors. During ►**fictive locomotion** (i.e. in the absence of sensory information), there is a tonic PAD accompanied by an overall synaptic depression of group I, group II and cutaneous afferents. Depression of group I afferent transmission is associated with the reductions in gain of stretch reflexes and the H-reflex observed at the onset of locomotion in humans. Superimposed on the tonic PAD, there are phase-dependent fluctuations of the membrane potential in group I, group II and cutaneous afferents, with more depolarization during the flexion phase. Synaptic transmission from group I, group II and cutaneous afferents also displays a phase-dependent modulation during fictive locomotion. However, unlike the synaptic depression observed during tonic PAD, phase-dependent PAD is not correlated with a depression of synaptic transmission from Ia afferents onto motoneurons. Both tonic and phase-dependent oscillations of PAD are mediated by as yet unknown mechanisms [9].

PAD evoked by stimulation of sensory afferents is also rhythmically modulated during fictive locomotion, suggesting that the locomotors central pattern generator (CPG) circuitry has access to the pathways mediating PAD (Fig. 3). The pattern of modulation of sensory evoked-PAD is complex and appears to depend more on the specific postsynaptic targets than on the peripheral origin of the afferents. During real as opposed to fictive locomotion, the patterns of PAD depend on interactions between supraspinal, sensory feedback and CPG inputs on pathways mediating PAD. PAD-related PSI mechanisms play an important role during patterning generation and contribute in shaping motor pattern activity to adapt limb movements to the environment [9].

During voluntary muscle contractions in humans there is a decrease of PSI of afferent terminals contacting the active motoneurone pools and a concomitant enhancement of PSI of afferent terminals ending on inactive motoneurone pools. These observations indicate that corticospinal control of PSI selectively “opens” transmission in group Ia afferents to voluntarily activated motoneurons, while “closing” transmission to motoneurons of relaxed muscles [10]. Findings in humans are supported by studies in the cat showing that different collaterals of the same afferent fiber are selectively controlled by separate sets of last-order

interneurons mediating PAD (Fig. 2) [8]. The differential PAD-related PSI of individual collaterals of muscle afferents allows a selective control of sensory information according to the neuronal targets and to the motor task to be performed [8,10].

References

1. Frank K, Fortes MGF (1957) Presynaptic and postsynaptic inhibition of monosynaptic reflexes. *Fed Proc* 16:39–40
2. Eccles JC (1964) Presynaptic inhibition in the spinal cord. *Prog Brain Res* 12:65–91
3. Rudiment P, Schmidt RF (1999) Presynaptic inhibition in the vertebrate spinal cord revisited. *Exp Brain Res* 129:1–37
4. Alvarez-Legman FJ, Nana A, Marquez S (1998) Chloride transport, osmotic balance, and presynaptic inhibition. In: Rudiment P, Room R, Mendel L (eds) *Presynaptic inhibition and neural control*. Oxford University Press, New York, pp 50–79
5. Engelmann HS, McDermott AB (2004) Presynaptic ionotropic receptors and control of transmitter release. *Nat Rev Neurosci* 5:135–145
6. Russo RE, Delgado-Lucama R, Hungary J (2000) Dorsal root potential produced by a TTX-insensitive microcircuitry in the turtle spinal cord. *J Physiol* 528:115–122
7. Lomeli J, Quevedo J, Linares P, Rudomin P (1998) Local control of information flow in segmental and ascending collaterals of single afferents. *Nature* 395:600–604
8. Jankowska E (2001) Spinal interneuronal systems: identification, multifunctional character and reconfigurations in mammals. *J Physiol* 533:31–40
9. Rossignol S, Dubuc R, Gossard JP (2006) Dynamic sensorimotor interactions in locomotion. *Physiol Rev* 86:89–154
10. Pierrot-Deseilligny E, Burke D (2005) Presynaptic inhibition of Ia terminals. In: Pierrot-Deseilligny E, Burke D (eds) *The circuitry of spinal cord*. Cambridge University Press, England, pp 337–383

Presynaptic Proteins

MICHAEL SEAGAR

INSERM/Université de la Méditerranée, UMR641, Faculté de Médecine Nord, Marseille, France

Definition

Proteins that participate in neurotransmission by ensuring functions specific to the presynaptic compartment (i.e., nerve terminals). Typically, these proteins control the progression of synaptic vesicles through the steps (docking, priming, vesicle fusion) that lead up to the release of neurotransmitters into the synaptic cleft.

Characteristics

Nerve terminals concentrate neurotransmitters in synaptic vesicles. Neurotransmitter release into the synaptic cleft then occurs when Ca^{2+} influx triggers the fusion of these vesicles with the presynaptic plasma membrane. However, only a small fraction of the total vesicle population within a nerve terminal is available to respond to the Ca^{2+} signal [1]. The presynaptic proteins described in this section, control transmitter release by holding vesicles in reserve or alternatively preparing and then accomplishing fusion.

Synaptic SNARE Proteins and SNARE Complexes

Vesicle fusion involves assembly of *trans* SNARE complexes at the interface between a docked synaptic vesicle and the plasma membrane, a process that pulls the opposing membranes together. These *trans* complexes contain three proteins: one vesicle protein, the vesicular- or v-SNARE VAMP 2 (also known as *synaptobrevin*) and two plasma membrane proteins, the target- or t-SNAREs: *syntaphin 1* and *SNAP-25* [1,2]. VAMP and syntaphin have a similar topology with membrane anchors at their C-terminal extremities and the N-termini orientated towards the cytoplasm. SNAP-25 is attached to the membrane via palmitoylation of amino acids located in the middle of the sequence, thus both its N- and C-termini are cytoplasmic. SNARE proteins carry a characteristic 70 amino acid sequence, the SNARE motif. This sequence mediates the interactions with partner SNAREs to form complexes [3]. SNAP-25 has two SNARE motifs while VAMP and syntaphin have only one each.

The N-terminal portion of syntaphin constitutes an auto-inhibitory domain, which folds back to interact with and mask the membrane-proximal helical (H3) domain containing the SNARE motif. In this “closed” conformation, syntaphin cannot bind to SNAP-25 and VAMP. When syntaphin “opens,” four SNARE motifs (1 from VAMP, 1 from syntaphin, 2 from SNAP-25) can assemble into a four-helical bundle forming the SNARE complex. In this bundle, the alpha helices are in a parallel orientation with all the N-termini at one end and all the C-termini at the other. Zipping-up of the complex, starting at the N-termini and progressing towards the C-termini pulls the C-terminal membrane anchors of v- and t-SNAREs, and consequently the vesicular and plasma membranes, towards each other. This leads to mixing of the outer lipid leaflet of the vesicle with the inner leaflet of the plasma membrane, and can then progress to full fusion upon Ca^{2+} influx. However, the SNARE proteins themselves do not directly bind Ca^{2+} . The fusion machine probably comprises of a radial array of SNARE complexes at the synaptic vesicle/plasma membrane interface, associated with Ca^{2+} -sensor proteins such as the synaptotagmins that confer Ca^{2+} -dependency on the release process.

The synaptic SNARE proteins are the targets of botulinum neurotoxins (of which there are seven distinct types: BoNT/A to G) and tetanus neurotoxin (TeNT) [4]. These extremely potent toxins inhibit transmitter release by introducing their light chains into the nerve terminal cytoplasm. The light chains are metalloproteases that specifically cleave synaptic SNAREs at defined peptide bonds (e.g., BoNT/B & TeNT - VAMP2, BoNT/A & E - SNAP-25, BoNT/C - syntaphin 1). BoNTs and TeNT do not affect vesicle docking but block synaptic vesicle fusion by a selective proteolytic attack on the fusion machine.

In addition to driving membrane fusion, *trans* v-SNARE/t-SNARE pairing may also contribute to proofreading, ensuring that vesicles can only fuse with the appropriate target membrane. Families of SNAREs have been identified in many other subcellular compartments in a variety of eukaryotic cells. Vesicular transport thus uses the same basic fusion machinery, conserved through evolution from yeast to human nerve terminals.

Presynaptic proteins include several molecules that bind to SNARE proteins and regulate the assembly of SNARE complexes.

Munc-18

Munc-18 (also called *nsec1* or *rbsec1* in mammals) is a 67 kDa hydrophilic protein, which associates with nerve terminal membranes via its interaction with syntaphin 1. *Munc-18* genes are the mouse members of the SM (*Sec1/Munc-18*) gene family, which includes yeast *Sec1* and the nematode and drosophila orthologues *Unc-18* and *Rop* [5]. The precise mode of action of *Munc18* is unknown. *Munc-18* binds tightly to the “closed” conformation of syntaphin 1 preventing SNARE complex assembly *in vitro*, but it is not simply a negative regulator of vesicle fusion. Genetic manipulations that decrease SM protein levels generally diminish secretion, consistent with the notion that these proteins are required for fusion. Yeast *SEC1* was initially identified as a gene required for exocytosis. However, in contrast to *Munc-18*, *sec1p* does not bind to monomeric yeast syntaphins but only to assembled SNARE complexes. SM proteins may act as chaperones to favor SNARE complex formation. Thus, although *Munc-18* binds to “closed” syntaphin, it might, in concert with additional factors, be involved in opening it and thus participate in priming. *Munc-18* binds to additional presynaptic proteins including the *Munc* interacting proteins (*Mint 1* and *2*). *Mints* link the vesicle fusion apparatus to adhesive proteins in the presynaptic plasma membrane that are involved in establishing synaptic connections.

Munc-13

Munc-13 proteins constitute a family of three high molecular weight (200 kDa) molecules. *Munc13-1* and

Munc13-3 are brain specific, while Munc13-2 is ubiquitous. At the N-terminal extremity, Munc-13 contains a conserved Ca^{2+} -dependent calmodulin binding site followed by a C1 motif, which binds the lipid messenger diacylglycerol, and two C2 domains [6,7]. Munc-13 (Unc-13 in the nematode) is involved in synaptic vesicle priming. Gene deletions in both mice and nematodes principally affect the readily releasable pool of synaptic vesicles. Munc-13 probably acts by binding to the auto-inhibitory N-terminal domain of syntaxin 1. In the nematode Unc13 displaces Unc-18, which is bound to the closed state of syntaxin. Furthermore, expression of mutant syntaxin, frozen in a permanently open conformation, rescues worms with an Unc-13 mutation. Thus, munc-13 appears to act downstream of munc-18 by driving syntaxin from a closed to an open conformation. Regulation of Munc-13 action via Ca^{2+} /calmodulin or diacylglycerol binding has been implicated in presynaptic plasticity.

Synaptophysin

► **Synaptophysin** was the first synaptic vesicle membrane protein to be isolated and cloned [8]. It is a major component of synaptic vesicles, thus anti-synaptophysin antibodies are widely used in immunocytochemistry to identify nerve terminals, and to evaluate diagnostically the neuroendocrine phenotype of a variety of tumors. Synaptophysin is an N-glycosylated 38 kDa protein. Like its homologue physins, synaptoporin, pantophysin and mitsugumin 29, it contains four membrane-spanning segments with N- and C-termini orientated towards the cytoplasm. It is the major cholesterol-binding protein in synaptic vesicles, and may contribute to the induction of vesicle curvature during vesicle biogenesis. Synaptophysin forms a complex in the vesicle membrane with the v-SNARE VAMP and subunits of the vacuolar proton pump (V-ATPase). The synaptophysin – VAMP2 complex prevents VAMP from entering into SNARE complex assembly. It thus constitutes an additional molecular mechanism for regulating transmitter release by determining v-SNARE availability. The amount of VAMP sequestered by synaptophysin is modulated by neuronal activity, indicating that it is functionally implicated in plasticity. However, deletion of the synaptophysin gene in mice does not result in a significant phenotype, which may reflect compensation by other members of the physin family. Mice that lack both synaptophysin and the structurally related tetraspan vesicle protein synaptogyrin do display defects in synaptic plasticity.

Additional presynaptic proteins mediate interactions of synaptic vesicles with the cytoskeletal elements. In this way, they seem to retain vesicles in a reserve pool that does not participate in regular vesicle exo-endocytotic recycling, unless mobilized by intense stimulation.

Synapsins

► **Synapsins** are neuron-specific phosphoproteins that are among the most abundant synaptic vesicle proteins. Three synapsin genes (I-III) have been identified in mammals; each undergoes differential splicing to yield at least nine isoforms [1]. The N-terminal domains of synapsins are highly conserved, containing sites for phosphorylation by cAMP- and Ca^{2+} /calmodulin-dependent protein kinase while the C-terminal portions are variable. The central domain, which accounts for more than half the sequence, forms multimers and binds ATP. This region has structural similarities to some ATPases, suggesting that synapsin may have enzymatic activity requiring ATP.

Neither deletion of the single synapsin gene in the *Drosophila* genome, nor the deletion of individual synapsin genes in the mouse genome, has strong effects on synaptic transmission. Deletion of all three synapsin mouse genes is not lethal but does affect behavior. It induces changes in synaptic transmission and plasticity that differs in excitatory versus inhibitory synapses. The functions of the synapsins are unclear, but may include recruiting synaptic vesicles to a reserve pool. Synapsins associate with the surface of vesicles, and bind to both vesicular phospholipids and proteins. They also interact with cytoskeletal proteins including actin, spectrin and tubulin. These binding reactions are regulated by phosphorylation. Synapsins thus seem to be involved in tethering vesicles to the cytoskeleton and defining a reserve pool that is not immediately available for docking and fusion. Synaptic activity leads to phosphorylation of synapsins, which dissociate from vesicles allowing their mobilization and migration to the plasma membrane to prepare for fusion. However, synapsins may have additional functions. Mice with deleted synapsin I and II genes show a global decrease in the number of synaptic vesicles, suggesting that synapsins play a role in stabilizing vesicles. Finally, synapsins may also act at a step closer to fusion by regulating priming or fusion competence.

Synaptic Vesicle Protein 2 (SV2)

► **SV2** is a synaptic vesicle glycoprotein of about 90 kDa, containing twelve potential transmembrane segments and N- and C-termini oriented towards the cytoplasm [1]. Sequences linking transmembrane regions are fairly short, although one highly glycosylated intraluminal loop is considerably larger. The sugar chains in this loop may contribute to the intravesicular matrix that is thought to bind neurotransmitters. Three SV2 genes in vertebrates encode homologous SV2A, SV2B and SV2C proteins that display distinct expression patterns in the brain, although SV2A is present in most neurons. The transmembrane and cytoplasmic linker sequences are

highly homologous between different SV2s, whereas the N-terminal domain and the intraluminal linkers diverge.

SV2s have significant homology to the Major Facilitator Superfamily of transporters for organic anions and cations, phosphates and sugars, and were initially thought to be transporters of neurotransmitters. However, their ubiquitous distribution rules out this possibility and indicates that they fulfill a more general function common to all synaptic vesicles. This function is still unknown, although a reasonable hypothesis is that they transport an unidentified substrate from the cytoplasm into the vesicle lumen.

Mice with deletions of the SV2A gene and the double SV2A/SV2B knockout display severe seizure activity and die postnatally. Cultured neurons from knock-out mice display increases in Ca^{2+} -dependent synaptic transmission that can be blocked by buffering cytoplasmic Ca^{2+} . Lack of SV2 thus seems to lead to abnormally high cytoplasmic Ca^{2+} levels. SV2 might therefore be involved in Ca^{2+} transport into synaptic vesicles to counterbalance the effects of burst firing in the nerve terminal. Furthermore, the N-terminal domain of SV2 interacts with, and may regulate the function of, the synaptic vesicle calcium sensor protein synaptotagmin. SV2 also constitutes the binding site for the anti-epileptic drug levetiracetam (KEPPRA), which perhaps enhances the ability of SV2 to limit electrical hyperexcitability [9].

Pathology

Botulism and Tetanus

These two potentially fatal diseases result from the inhibition of neurotransmitter release by BoNT and TeNT, which proteolyze presynaptic SNARE proteins. BoNT and TeNT are produced by the soil-borne bacteria *Clostridium botulinum* and *Clostridium tetani* [4]. Human botulism, mainly due to BoNT serotypes A, B and E, is typically caused by either eating contaminated food, wound infection, or in infants by intestinal proliferation of ingested clostridial spores. Botulism is a flaccid paralysis with classic symptoms: double/blurred vision, drooping eyelids, slurred speech, difficulty in swallowing, dry mouth, and muscle weakness. In severe cases, death can result from respiratory failure. Tetanus, which typically results from contamination of a deep puncture wound with *C. tetani*, involves muscular hypercontraction with symptoms including headache, muscular stiffness in the jaw (lockjaw) and neck, difficulty in swallowing, rigidity of abdominal muscles, spasms, sweating, fever and convulsions.

The differences between botulism (flaccid paralysis) and tetanus (muscle contractions and spasms) are due to differences in the neuronal populations affected. BoNT inhibits motoneurone terminals, blocking acetylcholine release and subsequent muscle contraction. In contrast,

TeNT acts specifically on inhibitory neurones in the spinal cord, diminishing tonic inhibition that indirectly activates acetylcholine release from motoneurones inducing muscle contractions.

Therapy

BoNTs (usually BoNT/A or B) are used as therapeutic agents that can be injected into muscles to reduce hypercontractions in dystonia, blepharospasm, strabism and a multitude of other indications. They are also widely used cosmetically (e.g., Botox) to reduce the muscle activity that underlies facial wrinkles.

References

1. Sudhof TC (2004) The synaptic vesicle cycle. *Annu Rev Neurosci* 27:509–547
2. Sollner T, Whiteheart SW, Brunner M, Erdjument-Bromage H, Geromanos S, Tempst P, Rothman JE (1993) SNAP receptors implicated in vesicle targeting and fusion. *Nature* 362:318–324
3. Sutton RB, Fasshauer D, Jahn R, Brunger AT (1998) Crystal structure of a SNARE complex involved in synaptic exocytosis at 2.4 Å resolution. *Nature* 395:347–353
4. Turton K, Chaddock JA, Acharya KR (2002) Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. *Trends Biochem Sci* 27:552–558
5. Toonen RFG, Verhage M (2003) Vesicle trafficking: pleasure and pain from SM genes. *Trends Cell Biol* 13:177–186
6. Gerst JE (2003) SNARE regulators: matchmakers and matchbreakers. *Biochim Biophys Acta* 1641:99–110
7. Junge HJ, Rhee JS, Jahn O, Varoqueaux F, Spiess J, Waxham MN, Rosenmund C, Brose N (2004) Calmodulin and Munc13 form a Ca^{2+} sensor/effector complex that controls short-term synaptic plasticity. *Cell* 118:389–401
8. Valtorta F, Pennuto M, Bonanomi D, Benfenati F (2004) Synaptophysin: leading actor or walk-on role in synaptic vesicle exocytosis? *Bioessays* 26:445–453
9. Lynch BA, Lambeng N, Nocka K, Kensel-Hammes P, Bajjalieh SM, Matagne A, Fuks B (2004) The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci USA* 101:9861–9866

Pretectal Area

Synonyms

► Area pretectalis

Definition

Situated immediately behind the superior colliculus, this nucleus plays a vital role in pupillary reflex and adaptation. Afferents come from the retina and

occipital cortical fields. Efferents go to the ipsi- and contralateral accessory oculomotor nucleus and superior colliculus.

The pretectal area includes the following nuclei: pretectal olivar nucleus, medial, anterior and posterior pretectal nuclei and optic tract nucleus.

► Mesencephalon

Pretectal Nuclei

Definition

Part of the subcortical visual shell. The pretectum consists of 7 nuclei in the visual midbrain, the n. of the optic tract, posterior limitans n., the olivary pretectal n., the anterior pretectal n., the posterior pretectal n., the medial pretectal n. and the commissural pretectal n. All connect substantially with the intergeniculate leaflet (IGL) and with each other.

They serve a variety of different functions. Perhaps the most well known is control of the pupillary light reflex by the olivary pretectal nucleus. This reflex is mediated by intrinsically photoreceptive retinal ganglion cells, as well as the classical rod/cone photoreceptors.

- Intergeniculate Leaflet
- Neural Regulation of the Pupil
- Photoreceptors
- Pupillary Light Reflexes
- Retinal Ganglion Cells

Pretectum

Definition

A midbrain region just rostral (forward) of the superior colliculus. It consists of a superficial nucleus (the nucleus lentiformis in frogs) containing migrated, large-celled neurons and a deep subnucleus. Cells of the nucleus lentiformis mesencephali are involved in horizontal optokinetic nystagm. Pretectal neurons respond more selectively to slowly moving vertical patterns, although horizontally sensitive neurons likewise been reported.

Directional information is encoded in a large population of motion-sensitive units, which includes

both narrowly and broadly tuned individual response profiles.

- Evolution of the Visual System: Amphibians
- Optokinetic Nystagmus
- Superior Colliculus

Prevertebral Ganglia

Definition

Prevertebral ganglia are autonomic ganglia that are found in the abdomen, around the origins from the aorta of the major vessels – the coeliac, superior mesenteric and inferior mesenteric arteries – and in the pelvis, close to the pelvic organs. The ganglia have various names applied to them the most common being: coeliac ganglia (also semi-lunar ganglia, solar plexus), superior mesenteric ganglia (inter-renal ganglia), inferior mesenteric ganglia and anterior (hypogastric) and posterior pelvic ganglia.

► Autonomic Ganglia

Prey-catching Behavior

Definition

Hunting animals show this type of behavior when trying to catch prey. This involves searching behavior, localization of prey and striking as well as killing of prey.

PRG

Definition

The Pontine Respiratory Group (PRG) is the region of respiratory neuron groups situated in the nucleus parabrachialis medialis (NPBM) and Kölliker-Fuse (KF) nuclei. The PRG is also termed as the pneumotaxic center.

► Respiratory Neurotransmitters and Neuromodulators

Primary Acoustic Cortex

Definition

Cerebral cortex areas in which the auditory tract terminates and which are involved in the first cortical processing steps for auditory signals. These include especially Brodmann areas 41 and 42 on the temporal plane.

► Telencephalon

One example is the posterior spinocerebellar tract which conducts impulses without interneurons from Clarke's nucleus of the thoracic cord to the cerebellar hemispheres.

► General CNS

Primary Afferent Depolarization (PAD)

Definition

A prolonged decrease in membrane potential usually produced by the activation of ionotropic GABA_A receptors at the presynaptic terminals of afferent fibers.

This depolarization is propagated antidromically in an electrotonic manner and can be detected either (i) directly by intra-axonal recordings of afferent fibers, (ii) as a dorsal root potential (DRP) from the central stump of a cut dorsal root filament, or (iii) as a positive potential (P wave) from the cord dorsum. Given that intra-axonal recordings are normally obtained in the dorsal horn, PAD recorded intra-axonally reflects the summed membrane potential changes occurring in all the collaterals of an individual afferent fiber.

PAD is accompanied by an enhanced excitability of afferent fiber terminals. Changes in excitability of intraspinal terminals can be estimated from threshold changes in response to intraspinal current pulses. The activation of pathways mediating PAD produces a threshold decrease and a consequent increase in amplitude of the antidromic compound action potential (Wall's technique).

► Action Potential
► GABA
► Presynaptic Inhibition

Primary Afferents

Definition

Primary afferents are tracts ascending without interneurons.

Primary Cultures

Definition

Primary cultures are the first stage of cell culture in which cells removed from tissue are cultured but before cells are removed from the primary culture to start the next culture.

Primary Hyperalgesia

Definition

Hyperalgesia at a site of injury or inflammation.

► Hyperalgesia and Allodynia
► Joint Pain

Primary Lateral Sclerosis (PLS)

Definition

PLS designates a syndrome of progressive upper motor neuron dysfunction and shows consistent differences from ► amyotrophic lateral sclerosis (ALS), which is characterized by progressive degeneration of both upper and lower ► motoneurons. Unlike ALS, which is familial in 5-10% of the cases, PLS appears to be sporadic in adults. Initially, stiffness is more prevalent in PLS than in ALS patients, but limb wasting, pronounced in ALS patients, is rare in PLS patients. ► Spasticity is the most prominent sign in PLS. Cortical atrophy is most pronounced in the ► precentral gyrus and expands into the ► parietal-occipital region. The course of PLS is very slowly progressive.

► Amyotrophic Lateral Sclerosis (ALS)

Primary Motor Cortex (M1)

Definition

A part of the cerebral cortex that is most directly involved in controlling the activity of motoneurons. In primates, primary motor cortex is located in the precentral gyrus of the frontal lobe just anterior to the central sulcus. An orderly representation of movements by body part exists within primary motor cortex. From medial to lateral the representation is lower extremity, trunk, upper extremity, face and tongue. Many corticospinal neurons in primary motor cortex make monosynaptic linkages with motoneurons. A distinctive feature of primary motor cortex is the presence of large pyramidal cells (Betz cells) in cortical layer V.

► [Motor Cortex: Output Properties and Organization](#)

Primary Progressive Aphasia

Definition

Presenile progressive degenerative disorder characterized by initially isolated loss of language abilities for at least two years, but mostly transcending into muteness and ► [dementia](#) (often ► [frontotemporal dementia](#)). It is due to a degeneration of cerebro-cortical regions around the ► [sulcus lateralis \(Sylvii\)](#) of the left hemisphere. The most frequent variants are: (i) progressive non-fluent aphasia (characterized by labored speech, agrammatism); (ii) semantic aphasia (characterized by loss of word and object meaning and dyslexia); (iii) logopenic progressive aphasia (characterized by word-finding problems and impaired sentence comprehension).

Primary Reinforcer

Definition

Sensory stimulus with intrinsic rewarding properties such as food or water.

► [Operant Conditioning](#)

Primary Sjögren's Syndrome

Definition

A chronic, multisystem autoimmune disorder characterized by dryness of mouth and other mucous membranes that occurs in the absence of an associated rheumatic disease (secondary Sjögren's syndrome) and may involve extraglandular manifestations such as arthralgias, Raynaud's syndrome, pulmonary involvement, renal tubular acidosis, peripheral and central nervous system (CNS) disease.

► [Central Nervous System Disease in Primary Sjögren's Syndrome](#)

Primary Somatosensory Cortex (S1)

Definition

Primary somatosensory cortex comprises four cytoarchitectonic regions, areas 3a, 3b, 1 and 2 (going from rostral to caudal), located in the anterior portion of the parietal lobe. Each region has a complete representation of the body. Areas 3a and 2 receive inputs mainly from deep receptors (the hand representation is characterized by receiving inputs from both skin and deep receptors), while neurones in areas 3b and 1 largely respond to skin stimulation.

► [Somatosensory Cortex I \(SI\)](#)

► [Somatosensory Cortex, Plasticity](#)

Primary Visual Cortex

Definition

Cerebral cortex in the occipital lobe of the mammalian brain.

The primary visual cortex (also known as Brodmann area 17, V1 or striate cortex) is the principal site at which visual information enters the cortex. It lies in the calcarine sulcus of the occipital lobe and receives visual signals from the retina relayed via the lateral geniculate nucleus (LGN) of the thalamus. Efferent projections

terminate in various visual areas in the cortex. Primary visual cortex has a complete map of visual space.

- Geniculo-Striate Pathway
- Striate Cortex Functions
- Evolution of the Visual System: Mammals-Color Vision and the Function of Parallel Visual Pathways in Primates

Priming

Definition

Priming refers to the effect where a prior exposure to a stimulus exerts influences on a subsequently given stimulus. Typically, priming produces a faster and/or a more accurate response to a stimulus associated with a previously presented stimulus called prime.

- Latent Learning
- Long-Term Memory

Primordium Hippocampi

- Evolution of the Pallium: in Amphibians

Principle of Neurological Minimization

Definition

Underlies responses of the neuromuscular system to changes in control variables and/or external forces; a tendency of system's elements to minimize, in the limits defined by neural, biomechanical and environmental constraints, the imposed activity by returning the system to the same or bringing it to a new steady state, depending on conditions; a solution to the redundancy problem.

- Equilibrium Point Control

Principle of Virtual Work

MARCELO EPSTEIN

Schulich School of Engineering, University of Calgary, Calgary, AB, Canada

Definition

From the physical point of view, the ►principle of virtual work is an attempt to characterize unequivocally an equilibrium ►configuration of a mechanical system (as defined in statics (q.v.)) by observing how it reacts to a small kinematical perturbation, called a *virtual displacement*.

Description of the Theory

In ►classical mechanics (q.v.), a mechanical system is defined from the kinematical point of view by means of its *configuration space*, whose dimension is an expression of the number of *degrees of freedom* of the system. A (local) system of coordinates in the configuration space is known as a set of *generalized coordinates*. It is important to stress that the generalized coordinates $q^i (i = 1, \dots, n)$ are mutually independent, since they already incorporate any geometrical constraints that the system may have. In the case of the double planar pendulum discussed in the article on classical mechanics (q.v.), for example, the number of degrees of freedom of the system is exactly two and so is the number of its generalized coordinates, whether the angular deviations from the vertical or any other set of appropriate geometrical parameters that are mutually independent and sufficient to define a state of the system are chosen. Another way to state this independence is to say that any description of a possible configuration of the system by means of coordinates, $x^I (I = 1, \dots, n' > n)$ say, can be eventually boiled down to n' (smooth) functions of n generalized coordinates:

$$x^I = x^I(q^1, \dots, q^n), \quad (I = 1, \dots, n'). \quad (1)$$

In the case of the planar double pendulum, a system of Cartesian coordinates may be chosen and an arbitrary configuration of the system expressed by means of the two pairs of coordinates, each corresponding to the position of one of the two masses. Thus, in this simple case, $n' = 4$. Nevertheless, it is clear that (given the lengths of the two links) all four Cartesian coordinates can be expressed in terms of the two angles, q^1 and q^2 , formed by the links and the vertical direction. The original four coordinates are interdependent, since they must satisfy the two constraints imposed by the assumed rigidity of the links. The generalized coordinates, on the other hand, by their very nature, already take these constraints into consideration and can,

therefore, be varied independently without violating these constraints. A *virtual displacement* of a mechanical system consists precisely in a set of small (infinitesimal) perturbations or *variations* $\delta q^i (i = 1, \dots, n)$ of the generalized coordinates away from a given configuration $q^i (i = 1, \dots, n)$. The forces acting on the system, whether internal or external, will in general perform work on any given virtual displacement, a scalar quantity appropriately designated as *virtual work*. In many cases, however, the forces necessary to maintain the constraints will not perform any virtual work. For example, in the case of the pendulum it is clear that the constancy of the length of the links is physically attained by intermolecular forces, which result in an internal state of tension. The work of these tensile forces would be equal to the magnitude of the force multiplied by the change of length of the corresponding link. Since, by their very definition, virtual displacements *respect the geometrical constraints* (the constancy of the length of the links) the virtual work of these internal *forces of constraint* will vanish. For a different example, consider a body that is constrained to slide freely on a surface. As long as there is no friction, the force necessary to maintain the contact between the body and the surface will be perpendicular to the surface and, therefore, will perform no virtual work on any virtual displacement. If friction is considered, however, this will no longer be the case, and it is a philosophical point of view whether or not the frictional force should be called a force of constraint. Be that as it may, it is clear that by purposely defining a virtual displacement as a possible displacement of the system, namely one that respects its geometrical constraints, the virtual work of some forces will automatically cancel out. If therefore, an equilibrium configuration is characterized by means of some property of the virtual work, it will follow that the forces of constraint will automatically play no role in the determination of equilibrium, a feature that would be almost unthinkable in an approach based on the concept of a free-body diagram of statics (q.v.). The principle of virtual work, in fact, provides such a characterization.

According to the principle of virtual work, a mechanical system in classical mechanics (q.v.) is in an equilibrium configuration if, and only if, the virtual work of all the forces acting on the system vanishes *identically* for all possible virtual displacements that can be impressed away from this configuration. This principle, therefore, characterizes an equilibrium configuration as one for which the system is work-wise indifferent to small perturbations compatible with its constraints. It is important to notice that the principle of virtual work is not an equation but an identity. Only so can it be understood that a single scalar statement is equivalent to a number of vector equations. For consistency, the principle of virtual work, when applied to a rigid plate in two dimensions, will be shown to

deliver the classical equations of equilibrium. The plate is assumed to be free to move in the x - y plane (no other constraints) and to be acted upon by N concentrated forces $\mathbf{F}^\alpha (\alpha = 1, \dots, N)$ acting at points with coordinates $x_\alpha, y_\alpha (\alpha = 1, \dots, N)$. In this case, the two Cartesian coordinates, x_p and y_p , of a point P of the plate and the (counter-clockwise, say) angular deviation θ of a material line drawn in the plate from, say, the x -axis can be adopted as generalized coordinates. A virtual displacement consists of any arbitrary combination of variations $\delta x_p, \delta y_p, \delta \theta$. The virtual displacement of the point of application of the force $\mathbf{F}^\alpha$ is the vector with components:

$$(\delta x_p - (y_\alpha - y_p)\delta\theta, \delta y_p + (x_\alpha - x_p)\delta\theta), \quad (2)$$

so that the principle of virtual work can be stated as:

$$VW = \sum_{\alpha=1}^N F_x^\alpha (\delta x_p - (y_\alpha - y_p)\delta\theta) + F_y^\alpha (\delta y_p + (x_\alpha - x_p)\delta\theta) \equiv 0, \quad (3)$$

with an obvious notation. Since this is an identity, any combination of $\delta x_p, \delta y_p, \delta\theta$ may be chosen. Choosing first $\delta x_p \neq 0, \delta y_p = \delta\theta = 0$:

$$\sum_{\alpha=1}^N F_x^\alpha = 0. \quad (4)$$

The choice $\delta x_p = 0, \delta y_p \neq 0, \delta\theta = 0$ yields:

$$\sum_{\alpha=1}^N F_y^\alpha = 0. \quad (5)$$

Finally, the choice $\delta x_p = \delta y_p = 0, \delta\theta \neq 0$ yields:

$$\sum_{\alpha=1}^N -F_x^\alpha (y_\alpha - y_p) + F_y^\alpha (x_\alpha - x_p) = 0. \quad (6)$$

Equations 4, 5 and 6 are immediately recognized as the standard equations of equilibrium of a rigid body in two dimensions. In particular, Eq 6 is the equation of moment equilibrium around point P . Considering now the case in which the plate is hinged at point P by means of a frictionless hinge, the configuration space of the system becomes one-dimensional and the rotational coordinate θ is a valid generalized coordinate. Obviously, in this case Eqs. 4 and 5 are no longer valid, and the equilibrium of the system is governed by Eq. 6 alone. Notice the essential difference with the conventional free-body diagram approach. In a free-body diagram the reactive forces at the hinge form an essential part of the package. The reactions thereat will intervene in the equations of equilibrium. In the virtual work approach, on the other hand, it is imperative not to disengage the plate from the hinge. Quite to the

contrary, the presence of the hinge, by reducing the number of degrees of freedom of the system, reduces the number of equilibrium equations. Naturally, this simple example alone would not justify the use of the principle of virtual work, but in more complicated situations its use, by eliminating the participation of reactive forces, results in a considerable simplification of the equations of equilibrium.

The virtual work expression can always be brought to the form:

$$VW = \sum_{i=1}^N Q_i \delta q^i, \quad (7)$$

by simply collecting all the terms that affect the variation of each generalized coordinate. The multipliers Q_i are called *generalized forces* and, in statics, can be at most functions of the generalized coordinates. The forces acting on a mechanical system are said to be *conservative* if there exists a scalar function V of the generalized coordinates such that:

$$Q_i = -\frac{\partial V}{\partial q^i}, i = 1, \dots, n. \quad (8)$$

This function, if it exists, is called a *potential energy* of the forces, and the forces are said to *derive from this potential* (which is determined uniquely up to an additive constant). It is important to realize that the property of the forces being conservative is independent of the particular choice of generalized coordinates, as can be verified easily by using the chain rule of differentiation. Combining Eqs. 7 and 8, it may be concluded that in a conservative system the virtual work of the forces can be calculated as the exact differential of the negative of the potential, namely:

$$VW = -\delta V. \quad (9)$$

The principle of virtual work for conservative systems establishes, therefore, that the potential energy is *stationary* at a position of equilibrium. It can be shown that the equilibrium is *stable* if the potential energy attains a strict *minimum* at the equilibrium configuration. A simple example is that of a cherry at the bottom of a wine glass (stable equilibrium, minimum gravitational potential energy), as opposed to a ball at a mountaintop (unstable equilibrium, maximum gravitational potential energy). The idea of virtual displacements as small perturbations of a putative equilibrium configuration is particularly clear in such simple examples.

In the case of continuum mechanics (q.v.), the principle of virtual work is also applicable provided the so-called *internal virtual work* is carefully accounted for, that is the work of the stress tensor upon the small virtual variations $\delta \mathbf{F}$ of the *deformation*

gradient. To see how this thought can be formalized, the Lagrangian equation of equilibrium is obtained from the Lagrangian equation of balance of *linear momentum* (Eq. 15 in *balance laws* (q.v.), whose notation is adopted) by eliminating the *acceleration* terms as:

$$T_{i,j}^I + B^i = 0. \quad (8)$$

Multiplying this equation by a *virtual displacement field*, that is, a field of the form $\delta x^i(X^1, X^2, X^3)$ and integrating over the referential volume of the body:

$$\int_{\Omega} (T_{i,j}^I + B^i) \delta x^j d\Omega = 0, \quad (9)$$

where the summation convention is used. This equation is obviously valid for any virtual displacement field. Considering the first term, the divergence operator is eliminated by invoking the divergence theorem. The price to pay is the appearance of a term at the boundary. Indeed:

$$\begin{aligned} \int_{\Omega} T_{i,j}^I \delta x^j d\Omega &= \int_{\Omega} (T_{i,j}^I \delta x^j)_{,i} d\Omega - \int_{\Omega} T_{i,j}^I \delta x^j_{,i} d\Omega \\ &= \int_{\partial\Omega} T_{i,j}^I \delta x^j N_i dA - \int_{\Omega} T_{i,j}^I \delta F_{ij}^I d\Omega \\ &= 0. \end{aligned} \quad (10)$$

In the boundary integral the *surface traction* is immediately recognized, namely, $S_i = T_{ij}^I N_j$. Putting together the results of Eqs. 9 and 10 the identity:

$$\int_{\Omega} B_i \delta x^i d\Omega + \int_{\partial\Omega} S_i \delta x^i dA \equiv \int_{\Omega} T_{ij}^I \delta F_{ij}^I d\Omega. \quad (11)$$

is finally obtained.

The left-hand side represents the *external virtual work* (EVW) of the *body forces* and the surface tractions, while the right-hand side can be identified with the *internal virtual work* (IVW) of the (first Piola-Kirchhoff) stress. It is not difficult to reverse the steps of this derivation and conclude that the identical satisfaction of the principle of virtual work in the form:

$$EVW \equiv IVW, \quad (12)$$

is equivalent to the equations of equilibrium of a deformable continuum. No restrictions have been specified upon the virtual displacement fields. Assume, however, that the *deformation* of part of the boundary is prescribed (for example, part of the boundary is fully supported). Then, the virtual displacement fields must vanish at that part of the boundary. One of the useful features of the principle of virtual work in continuum mechanics is that it delivers not only the interior equations of equilibrium, but also the appropriate

boundary conditions of the problem. The Lagrangian formulation has been presented, but a similar treatment delivers also the Eulerian form of the principle. In this case, the internal virtual work is given by $IVW = \int_{\omega} t^{ij} \delta D_{ij} d\omega$.

In the case of a deformable continuum, the concept of potential energy can be extended to the stresses themselves. If the constitutive equation of the material is such that the [first Piola-Kirchhoff stress](#) tensor is derived from a scalar potential function of the deformation gradient, the material is said to be *hyperelastic* ([hyperelasticity](#)). Configurations of equilibrium can be associated with a stationary value of the total potential energy of the system.

References

1. Truesdell C, Toupin R (1960) The classical field theories. In: Flügge S (ed) Handbuch der Physik, vol III/1. Springer, Berlin, pp 226–793
2. Lanczos C (1970) The variational principles of mechanics, 4th edn. Toronto University Press, Toronto
3. Epstein M, Herzog W (1998) Theoretical models of skeletal muscle. Wiley, Chichester

Principle of Virtual Work

Definition

In analytical mechanics, the statement that the equilibrium of a system is equivalent to the identical vanishing of the work done by the external forces on all possible virtual displacements of the system.

► [Mechanics](#)

Prion (Proteinaceous Infectious Particle)

Definition

Prion (proteinaceous infectious particle) is a proteinaceous infectious agent that cause bovine spongiform encephalopathy (BSE) and human variant Creutzfeldt Jakob disease in humans.

► [Creutzfeldt-Jakob Disease](#)

Prism Adaptation

Definition

When a person wears laterally displacing prism glasses, he or she initially experiences difficulty in reaching an object. However, he or she soon adapts to the prism so that the object can be reached. Such a phenomenon is called prism adaptation, and involvement of the cerebellum in the adaptation is known.

► [Sensory Motor Learning/Memory and Cerebellum](#)

Probabilistic Inference

► [Bayesian Statistics \(with Particular Focus on the Motor System\)](#)

Procedural Learning

Definition

Training a sensori-motor task, such as playing the piano.

► [Sensory Plasticity and Perceptual Learning](#)

Procedural Memory

Definition

Memory of skill or movement improved by practice or experience is called the procedural memory. It has been regarded distinct from the declarative memory about episodes or notions etc. These two types of memories are supported with independent neuronal mechanisms.

Patients impaired in the declarative memory retain the unimpaired procedural memory and vice versa.

► [Long-Term Memory](#)

► [Sensory Motor Learning/Memory and Cerebellum](#)

Process S

► Sleep Homeostasis

Processing of Tactile Stimuli

HEATHER E. WHEAT, ANTONY W. GOODWIN
Department of Anatomy and Cell Biology, University
of Melbourne, Parkville, VIC, Australia

Definition

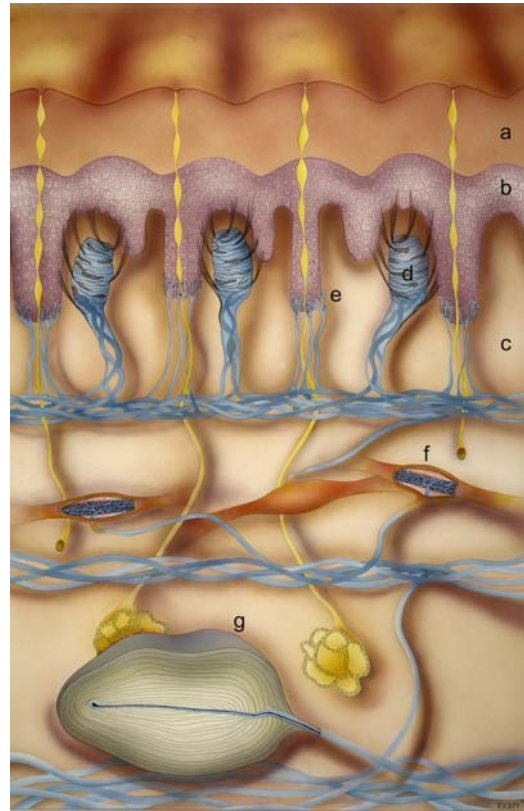
Tactile here refers to that which is concerned with the sense of touch or the perception of touch. When we touch or manipulate objects, four classes of low-threshold cutaneous mechanoreceptor sensors are activated by the stresses and strains arising from the interaction between skin and object. These four receptor types have different response characteristics because of differences in their structure and in their location in the skin. During manipulation, the receptor responses are determined by many different features of the manipulated object and of the hand movements. Such features include: contact or grip force, the presence of shear forces, the area and shape of the contact region, the surface texture, the shape and compliance of the object, and the presence of slip between the object and the skin. This information is conveyed to the central nervous system by mechanoreceptive afferents (peripheral nerve fibers) which innervate these mechanoreceptors. A population of mechanoreceptive afferents is able to simultaneously encode multiple stimulus parameters because each parameter has a different representation in the spatial and temporal patterns of activity across the afferent population.

Characteristics

Tactile Sensors of the Glabrous Skin

The glabrous (ridged) skin of the fingers consists of two main layers, an outer epidermis and an inner dermis, which are arranged in an interlocking pattern of grooves and ridges (Fig. 1).

Within the skin are thermoreceptors, nociceptors and low-threshold mechanoreceptors; these vary in structure from free nerve endings to mechanically complex end organs. In this chapter the focus is on the four low-threshold mechanoreceptors: Merkel cell-neurite complexes at the epidermal-dermal junction, Meissner corpuscles in the outer papillary layer of the dermis, and Pacinian and Ruffini corpuscles in the



Processing of Tactile Stimuli. Figure 1 A cross-section through glabrous skin. The upper layer, or epidermis (b), is covered in thick keratin (a). Both the epidermis and the underlying layer, the dermis (c), have a wave-like structure. Peripheral nerve fibers, shown in blue, terminate on four types of mechanoreceptors, the Meissner corpuscles (d), the Merkel endings (e), the Ruffini organs (f) and the Pacinian corpuscles (g). Reproduced with permission from Ian Darian-Smith.

deeper reticular layers of the dermis. These receptors are innervated by large-diameter myelinated nerve fibers, classified as A β fibers, which conduct action potentials rapidly. A single fiber may end in a single mechanoreceptor, but more commonly will innervate many mechanoreceptors. Conversely, a single mechanoreceptor may be innervated by a single fiber or by multiple fibers [1].

In humans, the fibers (also termed afferents) fall into four distinct groups classified by their response properties. Slowly-adapting type I (SAI) and slowly-adapting type II (SAII) afferents are associated with Merkel endings and Ruffini corpuscles respectively and respond to both the static and dynamic components of the stimulus. Fast-adapting type I and II (FAI and FAII) afferents are associated with Meissner corpuscles and Pacinian corpuscles respectively and respond only to dynamic components of the stimulus. Monkey

glabrous skin lacks SAI afferents, but the remaining three afferent types, common to humans and monkeys, have similar response properties in both humans and monkeys. Fast adapting afferents are also referred to as rapidly adapting afferents. The density of SAI and FAI afferents innervating the hand decreases proximally from a maximum at the fingertip of 0.7 mm^{-2} for SAI afferents and 1.4 mm^{-2} for FAI afferents. The proximo-distal gradient is less pronounced for SAII and FAII afferents which in the human fingertip have lower densities than the type I afferents (0.1 and 0.21 mm^{-2} respectively). The receptive fields of type I mechanoreceptive afferents (with more superficial receptors) are small and well demarcated whereas those of the type II afferents (with deeper receptors) are large and diffuse with some extending across the entire hand.

Tactile Sensors of the Hairy Skin

The mechanoreceptors of the hairy skin are either associated with the hairs on the skin or are situated between them. There are three hair types – specialized sinus or vibrissae (which are not present in humans), vellus or pelage, and guard. The hair follicles are innervated by: free nerve endings, Merkel nerve endings associated with SAI afferents, lanceolate nerve endings associated with rapidly-adapting afferents, and Ruffini corpuscles associated with SAII afferents. Most sinus hairs are also innervated by lamellated corpuscle of Pacinian type which are associated with rapidly-adapting afferents. Between the hair follicles are dome-like elevations, the so called “touch domes” or *Haarscheiben* of Pinkus which are innervated by slowly-adapting Merkel endings and free nerve endings [2].

Central Nervous System Pathways

The peripheral afferent nerve fibers described above are the peripheral processes of bipolar cells with cell bodies in the dorsal root ganglia, which lie in close proximity to the spinal cord. The central processes of these bipolar cells enter the spinal cord via the dorsal roots and it is at this point that axons conducting information from the low-threshold mechanoreceptive afferents become segregated from those carrying nociceptive or thermal information. The predominant spinal pathway for the low-threshold mechanoreceptive afferents is via the dorsal columns (cuneate and gracile fascicles); most axons enter the spinal cord and ascend to the brainstem without synapse.

The dorsal column axons project principally to, and synapse on, cells within the ipsilateral cuneate and gracile nuclei (the dorsal column nuclei) in the brainstem. Axons of cells in these nuclei cross to the other side of the brainstem and ascend as the medial lemniscus, synapsing primarily in the ventroposterior nuclear complex of the thalamus. The axons of these thalamic cells project predominantly to the primary

somatosensory cortices in the postcentral gyrus – Brodmann areas 3a, 3b, 1 and 2. Throughout, the ascending pathways are organized largely on somatotopic principles. Furthermore, neurons to this point retain many of the functional properties of their primary afferent input in terms of basic response functions and receptive field characteristics.

Overview of Tactile Processing

Tactile processing falls into two separate, but overlapping, broad categories. In the first category, touch informs pattern and form perception which allows us to identify objects. Such information includes the object's shape, size, softness and its surface texture. Commonly this is a conscious process. In the second category, touch forms a vital component of the sensorimotor integration that is essential for precision grip and effective manipulation. Object characteristics such as compliance and surface microgeometry, as well as task related characteristics such as position of contact on the skin, linear and torsional loads, and contact or grip forces are relayed by touch to the central nervous system, often without deliberate or conscious tactile perception. To assess what tactile information is signaled to and used by the brain, psychophysical measurements of the human capacity to detect, discriminate, scale and identify specific features of a stimulus have been conducted. Such behavioral studies provide an indication of the minimum information about a particular stimulus parameter that must be received by the brain for conscious perception. Many of these studies have been accompanied by neurophysiological experiments, employing the same stimuli, in order to determine how the essential stimulus parameters are represented in the responses of different neural populations.

The responses of single mechanoreceptive afferents innervating the skin have been recorded by inserting micro-electrodes through the skin into human peripheral nerves and by micro-dissection (fiber splitting) of monkey peripheral nerves. The response characteristics of the different afferent types will be discussed within the context of a range of functionally relevant parameters. Important to note is that all four low-threshold cutaneous mechanoreceptive afferent types are potentially activated by contact with an object but the extent to which each class contributes to the coding of essential task-related information varies depending on the stimulus and task parameters. Furthermore, for all but the simplest stimuli the parameters of the stimulus and task are only represented or encoded unambiguously in the responses of a population of fibers, and not in the responses of isolated single fibers. The studies described in the following sections are based on single fiber responses but for the most part, because of the manner in which the stimuli were presented, they can be extrapolated to represent population responses.

Neural Representation of Object and Task Parameters

Simple Stimuli

The principal value of simple stimuli, such as punctate probes indenting the skin or vibrating in and out of the skin, has been a clear-cut classification of the afferent types (Fig. 2). The temporal characteristics of the responses divide the afferents into slowly and fast adapting groups and the spatial characteristics (mainly size) of the receptive fields define the type I and type II groups. Thresholds of the responses correspond to human detection thresholds measured psychophysically.

Pattern and Form

The earliest measure of spatial resolution in the tactile system was the two-point limen, a simple but unreliable measure that underestimates the capacity of the system. More recently, tactile coding of spatial characteristics or fine form has been investigated using a range of relatively simple stimuli such as edges, bars and gratings as well as more complex patterns such as embossed letters and Braille-type characters [3]. Human psychophysics experiments are matched with single fiber recordings, commonly in monkeys and more rarely in humans. Such studies have found that SAI afferents resolve the spatial details of the stimuli with greater clarity than either FAI or FAII afferents in monkeys or FAI, FAII or SAII afferents in humans. Recognition and discrimination of patterned stimuli are enhanced when they are scanned across the finger, rather than pressed into the finger. This can be explained in part by the increased resolution in SAI responses when such stimuli are moved tangentially across the skin compared to stationary presentation. Variations in scanning speed and contact force have little effect on the spatial resolution of fiber responses or on human perception. Although there is strong evidence for the

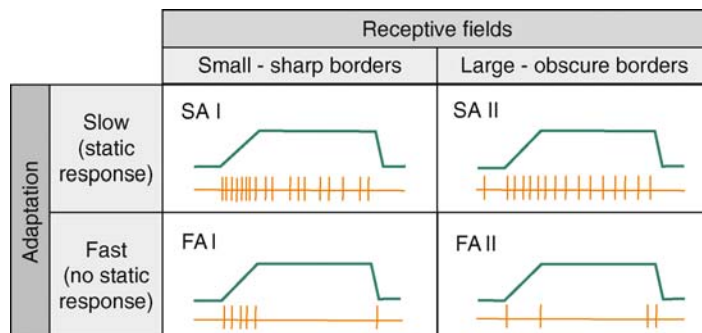
role of SAI afferents in encoding fine spatial detail, the other afferents do play a role, particularly the FAI afferents when there is lateral movement between the stimulus and the skin.

Texture

The most common perceptual descriptor of surface texture is the sensation of roughness. In early psychophysics experiments common materials, such as sandpaper, were used. More recent stimuli consist of precisely manufactured three-dimensional features, which can be defined mathematically. These allow quantitative neural studies, usually in monkeys, which can be compared with human psychophysics. Stimuli commonly used are either gratings of alternating grooves and ridges, or embossed dot arrays.

Perceived roughness increases monotonically with the spatial period of the texture up to spacings of around 3 mm for both gratings and dot arrays. The most critical feature underlying perceived roughness is the groove width for gratings and the dot spacing for dot arrays. Tangential movement between the stimulus and the skin affects roughness perception. The difference threshold for the spatial period of gratings is degraded from a threshold of 5% when there is movement to a threshold of 10% when there is no movement. Roughness perception is independent of whether the tangential movement is active or passive and is little affected by variations in the rate of movement, but perceived roughness increases when contact force increases [4].

Textures affect both the spatial and temporal patterns in peripheral neural population responses as well as intensive parameters like total neural response. How these population features are used by the central nervous system appears to depend on the nature of the stimulus and the task.



Processing of Tactile Stimuli. Figure 2 Classification of the four types of low-threshold mechanoreceptive afferent fibers innervating the glabrous skin of the human fingerpad. Upper trace (green) in each panel shows the indentation amplitude (vertical axis) as a function of time (horizontal axis) for a probe indented into the skin for 1 s. Traces below (orange) show neural responses; each vertical tick represents an action potential. Adapted with permission from Johansson RS and Vallbo AB (1983) Trends in Neuroscience 6:27–32.

Shape

The identification of an object's shape is essential for dexterous manipulation and often involves active exploration of the object. This brings into play a spectrum of sensory mechanisms which relay information about the position and movement of the joints in the hand and arm, as well as cutaneous tactile information. Objects range in shape from a simple sphere to the complex shapes of eating utensils and tools we routinely use. All shapes can be described in terms of their local curvatures. Shapes such as spheres, cylinders, and toroids can be quantified easily; this facilitates analysis of the neural representation of their shape and subsequent correlations with human performance. When simple shapes such as spheres are applied to the skin so that only cutaneous information can be utilized, humans are able to discriminate a difference in curvature (reciprocal of the radius) of the order of 10%. When spheres are indented into a monkey's fingerpad, a clear monotonic relationship exists between single fiber responses and stimulus curvature; both the SAI and FAI afferent responses are modulated but the effect is more pronounced and more reliable for the SAI afferents [5]. Comparable responses in human afferents to spheres and cylinders applied to the fingerpad have been reported; curvature significantly modulates responses in SAI, SAI, and FAI afferents.

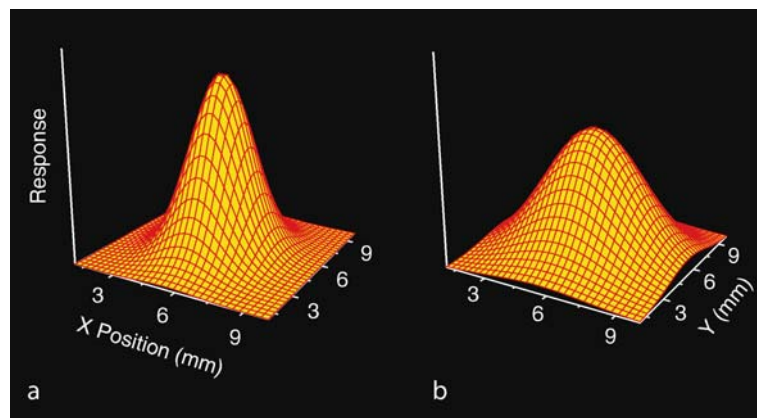
For any shape more complex than a sphere, more than one parameter is needed to define it. For example, a cylinder is defined by the orientation of its long axis and the radius or curvature in the orthogonal direction. A toroid is defined by three parameters – two orthogonal curvatures and an orientation. SAI afferent responses are monotonically related to the curvature of these

shapes and are modulated by stimulus orientation [6]. When stimuli such as toroids, cylinders and more complex arrays of alternating convex and concave cylindrical shapes of differing curvature are scanned across the monkey's fingerpad, both SAI and FAI afferent responses are modulated. FAI afferents however require higher stroke velocities to elicit responses. The major geometrical features of three-dimensional objects scanned across the skin such as spheres, cylinders and toroids varying in shape, orientation and stroke trajectory are reproduced in the spatiotemporal responses of SAI afferents and to a lesser degree FAI afferents.

When a complex shape is explored or handled, all the parameters of the stimulus and the manipulation affect the responses of individual primary afferent fibers. Nevertheless, independent information about each of the parameters is relayed to the central nervous system because each parameter is represented or encoded uniquely in the primary afferent population response (Fig. 3).

Manipulation

When we manipulate objects, the sensorimotor system optimizes the forces applied by the fingers. The motor control system must adopt forces that are sufficiently large to prevent slips but are not excessive in order to avoid fatigue and to ensure that delicate objects are not damaged. In addition, force magnitudes and directions must suit the shape of the object and the load conditions, and must take account of parameters such as friction. Also, the control system must rapidly and automatically adjust the grip forces to meet the demands imposed by any unexpected changes in loads during a task. Our ability to manipulate objects with dexterity is itself



Processing of Tactile Stimuli. Figure 3 Representation of object shape in an ideal SAI afferent population response. The stimuli are spherical with radii A, 1.44 mm (curvature 694 m^{-1}) and B, 3.9 mm (curvature 256 m^{-1}). The differences in object shape are reflected in the population response profiles. The smaller, more curved sphere (a) elicits a response profile which is narrower and more peaked than that elicited by the larger, less curved sphere (b). These response profiles will be distorted by the characteristics of real peripheral neural populations including the pattern of innervation and the responsiveness of the individual fibers.

testimony to the accuracy of the underlying sensorimotor control system. This is only possible because of sensory feedback from the hand, a large component of which arises from the cutaneous mechanoreceptive fibers. Studies which mimic the forces occurring in everyday manipulations, such as lifting a container of liquid and tilting it, show that humans are able to scale and discriminate, independently, forces acting normal to the skin surface (grip force), forces acting tangential to the skin (load force) and rotational forces (torques) [7]. The magnitudes and directions of these forces and torques are encoded in the responses of whole populations of peripheral afferents along with precise information about the shape of the object being manipulated and the positions of contact on the skin [8]. Such studies demonstrate that the mechanoreceptors in the glabrous skin of the digits provide a rich and accurate source of information during complex manipulations. This information underlies both feedforward and feedback motor control.

Representation in the Central Nervous System

Many of the object and task parameters discussed above have been used in studies of the response properties of cells in the somatosensory cortices of non-human primates [9]. Studies of single cells in somatosensory cortex SI have shown that responses reproduce essential object features presented to the skin and show response patterns similar in many cases to the primary afferent input signals. For example, the configuration of embossed dot ensembles is clearly evident in the response patterns across arrays of single cortical units. Some single cortical units have characteristics which appear to combine response characteristics of more than one afferent type, e.g., SAI and FAI afferents, providing an additional layer of information. The SII somatosensory cortex appears to have some higher level functions than SI, such as extracting the orientation of a stimulus independent of the position of contact on the finger [10]. How input from tactile sources is combined with other sources of sensory input such as afferents from the joints, muscles and hairy skin is not known but information from all of these sources are potentially important in controlling precise hand movements.

References

1. Darian-Smith I (1984) The sense of touch: performance and peripheral neural processes. In: Handbook of physiology. The nervous system III. American Physiology Society, Bethesda, MD, pp 739–788
2. Halata Z (1993) Sensory innervation of the hairy skin light- and electronmicroscopic study. *J Invest Dermatol* 101:75S–81S
3. Johnson KO, Hsiao SS (1992) Neural mechanisms of tactile form and texture perception. *Annu Rev Neurosci* 15:227–250

4. Sathian K (1989) Tactile sensing of surface features. *Trends Neurosci* 12:513–519
5. Goodwin AW, Wheat HE (2004) Sensory signals in neural populations underlying tactile perception and manipulation. *Annu Rev Neurosci* 27:53–77
6. Khalsa PS, Friedman RM, Srinivasan MA, LaMotte RH (1998) Encoding of shape and orientation of objects indented into the monkey fingerpad by populations of slowly and rapidly adapting mechanoreceptors. *J Neurophysiol* 79:3238–3251
7. Wheat HE, Salo LM, Goodwin AW (2004) Human ability to scale and discriminate forces typical of those occurring during grasp and manipulation. *J Neurosci* 24:3394–3401
8. Birznieks I, Jenmalm P, Goodwin AW, Johansson RS (2001) Encoding of direction of fingertip forces by human tactile afferents. *J Neurosci* 21:8222–8237
9. Tremblay F, Ageranoti-Belanger SA, Chapman CE (1996) Cortical mechanisms underlying tactile discrimination in the monkey. 1. Role of primary somatosensory cortex in passive texture discrimination. *J Neurophysiol* 76(5):3382–3403
10. Thakur PH, Fitzgerald PJ, Lane JW, Hsiao SS (2006) Receptive field properties of the macaque second somatosensory cortex: nonlinear mechanisms underlying the representation of orientation within a finger pad. *J Neurosci* 26:13567–13575

Progenesis

Definition

Paedomorphosis (retention of formerly juvenile characters by adult descendants during evolution) produced by precocious sexual maturation of an organism still in a morphologically juvenile stage.

► Evolution and Phylogeny: Chordates

Progenitor Cell

Definition

A progenitor cell is a cell maintaining its capacity for self-renewal and differentiation. Although the distinction between progenitor cells and stem cells is often ambiguous, the term “progenitor cell” includes undifferentiated cells with more limited plasticity and in some cases is used for cells in which multipotency is difficult to demonstrate.

► Adult Neurogenesis

Programmed Cell Death

HIROYUKI YAGINUMA

Department of Anatomy, School of Medicine,
Fukushima Medical University, Fukushima, Japan

Synonyms

Naturally occurring cell death; Physiological cell death;
Developmental cell death; PCD

Definition

► **Programmed cell death** (PCD) in the developing nervous system is defined as spatially and temporally reproducible and species-specific loss of large numbers of individual cells (neurons and glia) during development [1].

Characteristics

Types and Extent of PCD

Development of the neuronal cells can be divided into three phases, (i) proliferating neuronal precursors or founder cells, (ii) postmitotic young neurons before contacting their targets and (iii) maturing neurons after establishing synaptic contact with their targets. In early developmental stages, the neural tube consists of a population of proliferating cells organized into a pseudostratified columnar epithelium, known as the ventricular zone (VZ). Postmitotic young neurons derived from the VZ aggregate and mature between the VZ and the pial surface to form the intermediate zone (IZ). In some areas in the forebrain, such as the dorsal thalamus, a second proliferative zone, the subventricular zone (SVZ) is formed between the VZ and the IZ. In the cerebral cortex, young neurons derived from both the VZ and SVZ migrate through the IZ to form a cortical plate. Programmed cell death can be observed in all three phases of neuronal development [1,2].

After the generation of neuronal cells, glial cells differentiate from glial precursor cells that are derived from the VZ and SVZ. A considerable number of differentiated glial cells are also known to undergo PCD.

PCD of Neuronal Precursors

In the mouse embryo, PCD of proliferating precursor or founder cells can be observed as early as embryonic day (E) 8.5, when the closure of the neural tube is not yet completed. In early developmental stages, massive PCD occurs in specific regions of the developing neural tube. These include ventral and dorsal regions of the spinal cord, floor plate, neural crest, the lamina terminals, ventral region of the forebrain, dorsal region of the hindbrain and the optic vesicle [3,4]. Sporadic small

amounts of PCD continue to occur in the VZ and SVZ from early to later developmental stages. But because cell proliferation occurs at the same time, it is difficult to elucidate the quantity of PCD. Estimated amounts of PCD vary from 0.3% to more than 50% depending on the regions analyzed and the methods that were used to detect dying cells. However, since it is reported that inhibition of PCD of neuronal precursors resulted in malformations of the nervous system, such as exencephaly and spina bifida, cell death of proliferating neural precursors is significant for normal development.

PCD of Postmitotic Young Neurons

Although this type of PCD is less common, there are some examples. Approximately 25% of postmitotic motoneurons in the non-limb innervating cervical spinal cord die before they establish synaptic contact with their target muscles [5]. In the dorsal root ganglion and the retina, a significant percentage of postmitotic neurons die before their axons reach their targets [4].

PCD After Establishing Synaptic Contacts with the Targets

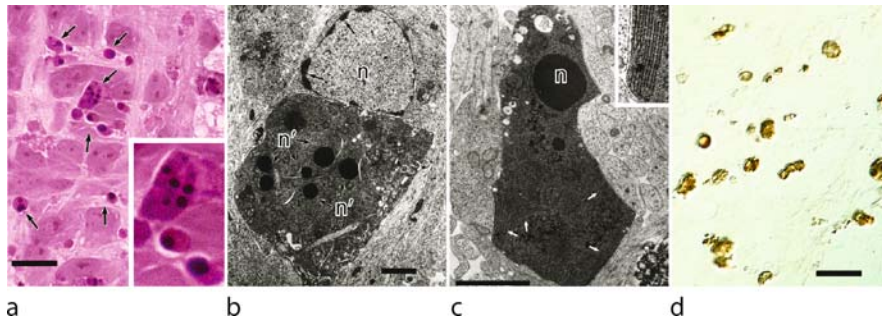
Neurons that have survived earlier phases of PCD begin to establish synaptic connections with other neurons and target cells. During this period, postmitotic differentiating neurons undergo PCD. This type of PCD has been found to occur virtually everywhere that it has been looked for and includes motoneurons, sensory neurons, autonomic neurons, retinal neurons, optic tectum, isthmo-optic nucleus, basal ganglia, cerebellum and cerebral cortex. Despite this widespread occurrence of PCD, it is also known that PCD does not occur in spinal interneurons and neurons in the medial and lateral pontine nuclei of the chick embryo. Quantitative analyses performed in the neuronal groups that are easily defined revealed that ~20–80% of postmitotic neurons undergo cell death. This type of neuronal death has been well studied and it is known that inadequate neurotrophic support derived from their targets, afferent inputs and other sources regulate this type of cell death [1].

PCD of Glial Cells

Both oligodendrocytes and astrocytes are known to undergo PCD. About 50% of oligodendrocytes normally die in the developing rat optic nerve and significant numbers of dying cells in the neonatal rat cerebellum are astrocytes [2].

In most cases, cells die by ► **apoptosis**. They shrink in size, the nuclear chromatin becomes pyknotic and condenses against the nuclear membrane (Fig. 1 a–c) and cytoplasmic organelles remain intact.

Eventually, the cytoplasm and nucleus break up into apoptotic bodies that are phagocytized and digested by macrophages or by adjacent healthy cells. In contrast to ► **necrosis (necrotic cell death)**, which is caused by



Programmed Cell Death. Figure 1 Light and electron micrographs of the ventral horn of the cervical spinal cord of the E4.5 chick embryo showing dying motoneurons. (a) Hematoxylin and eosin staining showing pyknotic dying neurons (arrows). *Inset* shows higher magnification of typical pyknotic neurons. (b, c) Electron micrographs showing typical examples of apoptotic degeneration. In the nucleus (*n*) of the upper cell in b, chromatin begins to condense against the nuclear membrane (arrows), suggesting that this cell is in the earliest stage of apoptosis. In the lower cell in b, the nucleus has been fragmented (*n'*) and the cytoplasm has become electron dense. The condensed nucleus and cytoplasm are conspicuous in the cell in (c). Aggregated ribosomes are often observed (arrows and insets in (c)). (d) TUNEL staining. Bar in (a) and (d), 10 µm. Bars in b and c, 2 µm.

acute cellular injury, apoptosis occurs as an ordered process without evoking inflammation. Another feature of apoptosis is nucleosomal DNA fragmentation and degradation. This can be observed in tissue sections by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) (Fig. 1d). The estimated time for the whole process of apoptosis is from a few hours to at most one half day.

Lower Level Processes

Intra-Cellular Mechanisms of PCD

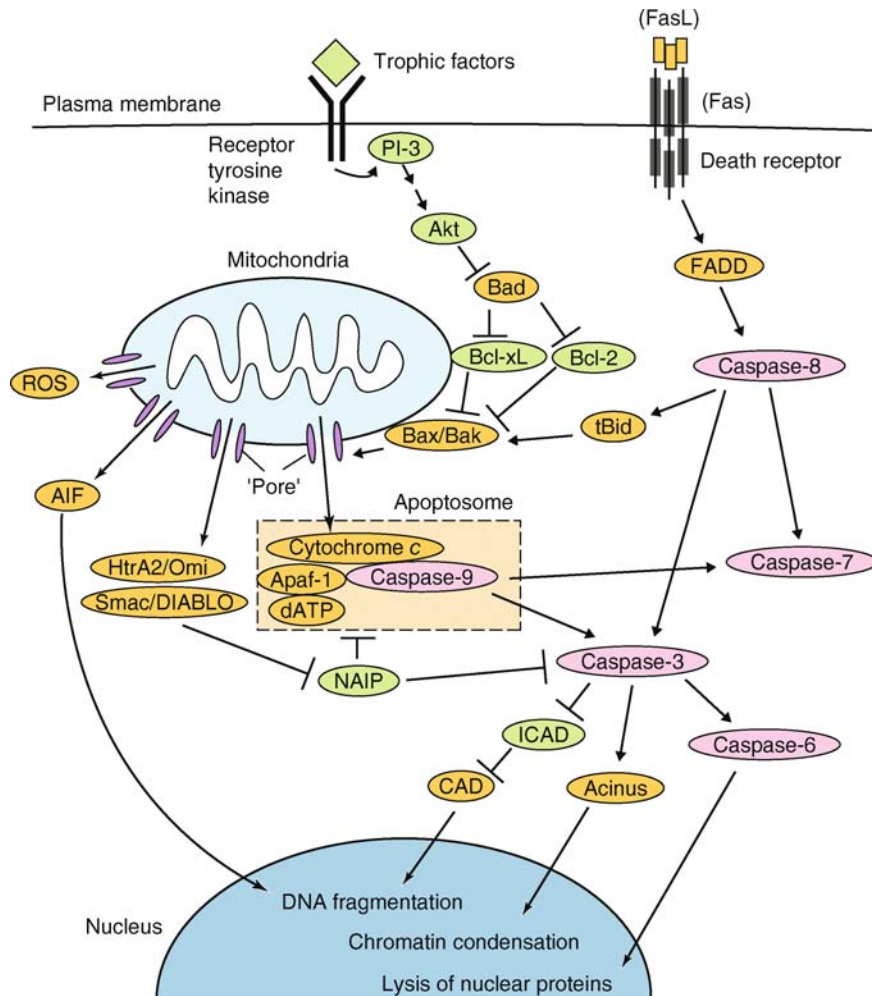
Cells in the developing nervous system share the same basic apoptosis mechanisms with all other cell types (Fig. 2).

The characteristic morphology of apoptosis is the result of activation of executioner **▶caspases**, such as caspases-3, -6 and -7. They activate a DNase (CAD) and acinus, which in turn cause DNA fragmentation and chromatin condensation (Fig. 2). Cytoplasmic and nuclear skeletal proteins are also cleaved by the executioner caspases, leading to cellular and nuclear shrinkage. The executioner caspases are activated by initiator caspases including caspase-8 and caspase-9. Caspase-8 and caspase-9 are activated through two different pathways, the death receptor pathway and the mitochondrial pathway, respectively. Association of a death receptor ligand (e.g. FasL) with its receptor (Fas) leads to recruitment of a death domain containing protein, FADD. This, in turn, recruits procaspase-8. Procaspase-8 undergoes auto-proteolysis to release active caspase-8 (Fig. 2). The key step in the mitochondrial pathway is the release of **▶cytochrome *c*** through pores formed in the mitochondrial outer membrane. Cytochrome *c*, **▶Apaf1**, procaspase-9 and ATP form the

apoptosome, which is a multimeric active holoenzyme that activates executioner caspases (Fig. 2).

▶Bcl-2 family proteins play fundamental roles in the process of mitochondrial pore formation. The Bcl-2 family consists of three subgroups, anti-apoptotic, pro-apoptotic and BH3-only proteins. When pro-apoptotic Bax or Bak is activated, they homo-oligomerize within the mitochondrial outer membrane to form large enough pores for cytochrome *c* release. Alternatively, Bax can change large channel proteins that reside in the outer mitochondrial membrane to allow cytochrome *c* to escape. Anti-apoptotic Bcl-2 family members, including Bcl-2 and Bcl-xL, can inhibit the effects of pro-apoptotic Bax or Bak through combining with them to form dimers. BH3-only proteins can bind to Bcl-2 and Bcl-xL to release pro-apoptotic, Bax or Bad, resulting in apoptosis. Therefore, BH3-only proteins serve as a key in the mitochondrial pathway (Fig. 2). It is also known that one BH3-only protein, Bid, can be cleaved (activated) by caspase-8 to form tBid, which in turn activates Bax and Bak. This allows cross talk between the two pathways (Fig. 2).

Besides cytochrome *c*, several other cell death-inducing molecules are known to escape through the pores formed in the outer mitochondrial membrane. These include **▶AIF (apoptosis inducing factor)**, EndoG (Endonuclease G), Smac/DIABLO and Omi/HtrA2. Reactive oxygen species (ROS) are also released from dysfunctional mitochondria. These molecules activate caspase-dependent or caspase-independent cell death pathways serving as initiators of collateral cell death pathways (Fig. 2). It is also known that there are intrinsic molecules that antagonize caspase activities to prevent apoptosis. These include **▶NAIP (Neuronal Apoptosis Inhibitory Protein)** and XIAP.



Programmed Cell Death. Figure 2 A simplified scheme of cell death pathways in cells in the developing nervous system. ►Caspases are indicated in pink, pro-apoptotic members in yellow, anti-apoptotic members in green. For details, see text.

Process Regulation

Inter-Cellular Regulation of PCD

Regulation by Trophic Factors (the Neurotrophic Theory)

The favored explanation as to why neuronal and glial cells die in the developing nervous system is “the neurotrophic hypothesis.” This proposes that developing neurons and glial cells require trophic support for survival and compete for a limited supply of trophic factors. Cells that cannot obtain enough trophic support undergo cell death. This hypothesis has been supported by many experimental studies in which the quantitative relations between neuronal groups and their synaptic targets or afferent inputs were altered. For example, removal of a limb bud on E2 in the chick embryo resulted in total disappearance of limb innervating motoneurons by E10 because of excessive motoneuron death. On the other hand, addition of a supernumerary limb bud resulted in the survival of more motoneurons.

Similarly, it has been proved that alteration of afferent inputs also affects the number of surviving neurons. However, it is not yet clear whether neurons compete for limited amount of trophic factors or limited sites where trophic factors are transferred to neurons. An important source of trophic support for developing neurons is their targets. In addition, signals derived from afferent inputs as well as from nonneuronal cells, such as central and peripheral glia, are recognized as possible sources of trophic regulation of cell death and survival.

Trophic factors that are required for survival of developing neurons vary depending on the neuronal population. For example, neurons in the sympathetic ganglia require target-derived NGF as a survival factor, whereas sensory neurons in peripheral ganglia require one or more of the ►neurotrophins, NGF, BDNF, NT-3 or NT-4/5. Several candidates for muscle-derived trophic

factors for motoneurons have been identified and include BDNF, NT-4/5, IGF, HGF, CT-1 and GDNF [1].

The binding of trophic factors to their specific receptors induces rapid protein phosphorylation and the activation of complex cascades of intracellular signals. Among them, the phosphatidylinositol 3-kinase (PI3-K)-Akt pathway is known to be directly involved in inhibition of cell death. Activated Akt phosphorylates the BH3-only protein, Bad. Phosphorylation of Bad dissociates Bad and the anti-apoptotic Bcl-2 family, Bcl-xL, allowing Bcl-xL to prevent cell death by blocking pore formation in the mitochondrial outer membrane (Fig. 2).

The neurotrophic hypothesis also proposes that the intrinsic default fate of developing neurons is to undergo PCD. Although the mechanism of the intrinsic cell death pathways is not known for most kinds of neurons, it has been suggested that the death receptor pathway that is activated by FasL and Fas may play a role in the PCD of motoneurons [6].

Regulation of Target-independent PCD

Little is known about the mechanisms that regulate PCD of proliferative precursor cells or young post-mitotic neurons. Since massive cell death of proliferative cells often occurs in specific regions of the neural tube, cell death may be the result of determination of regional specificity. In fact, following perturbation of sonic hedgehog signaling, which determines the regional specificity of the ventral half of the spinal cord, distribution of dying cells was altered [7]. Moreover, death-factor signaling may also induce early neuronal death. For example, in early retinal development, postmitotic young neurons are known to undergo cell death by NGF signaling through p75^{LNTN} and by TGF β , which are provided by macrophages and local surrounding cells respectively [8,9].

Function

Role(s) of PCD

Since perturbation of normal PCD results in various kinds of defects in the nervous system, cell death during development plays a significant adaptive role. Possible functions of cell death in the developing nervous system are:

1. Pattern formation and morphogenesis
2. System or size matching
3. Removal of cells of an appropriate phenotype or cells that have no function
4. Error correction
5. Removal of harmful cells that have defective DNA

Pathology

One genetic disease in humans in which cell death has been implicated is infantile p75^{LNTN} spinal muscular atrophy

(SMA). A clear link between SMA and failed inhibition of cell death has been proposed. In severe SMA, the neuronal specific inhibitor of apoptosis (IAP) family member known as NAIP is often dysfunctional due to missense and truncation mutations. IAPs such as NAIP potentially block the enzymatic activity of executioner caspases (3 and 7) suggesting that NAIP mutations may permit unopposed developmental apoptosis to occur in sensory and motor systems resulting in lethal muscular atrophy [1].

Since neurons need their targets for their survival, loss of one neuronal group or target tissue often results in a secondary loss of other neuronal groups. For example, the “cerebellless” mutant mouse lacks the entire cerebellar cortex. The primary defect is a specific inhibition of GABAergic neurons including Purkinje cells, resulting in secondary and complete loss of external germinal layer, pontine and olivary nuclei during development [10].

References

1. Oppenheim RW, Johnson JE (2003) Programmed cell death and neurotrophic factors. In: Squire LR, Bloom FE, McConnell SK, Roberts JL, Spitzer NC, Zigmond MJ (eds) *Fundamental neuroscience*. Academic Press, San Diego, SA, pp 499–532
2. Roth KA (2005) Programmed cell death. In: Rao MS, Jacobson M (eds) *Developmental neurobiology*. Kluwer Academic/Plenum, New York, pp 317–328
3. Kuan CY, Roth KA, Flavell RA, Rakic P (2000) Mechanisms of programmed cell death in the developing brain. *Trends Neurosci* 23:291–297
4. de la rosa EJ, de Pablo F (2000) Cell death in early neural development: beyond the neurotrophic theory. *Trends Neurosci* 23:454–458
5. Yaginuma H, Tomita M, Takashita N, McKay SE, Cardwell C, Yin QW, Oppenheim RW (1996) A novel type of programmed neuronal death in the cervical spinal cord of the chick embryo. *J Neurosci* 16:3685–3703
6. Raoul C, Pettmann B, Henderson CE (2000) Active killing of neurons during development and following stress: a role for p75^{NTR} and Fas? *Curr Opin Neurobiol* 10:111–117
7. Oppenheim RW, Homma S, Marti E, Prevette D, Wang S, Yaginuma H, McMahon AP (1999) Modulation of early but not later stages of programmed cell death in embryonic avian spinal cord by sonic hedgehog. *Mol Cell Neurosci* 13:348–361
8. Dechant G, Barde YA (2002) The neurotrophin receptor p75^{NTR} : novel functions and implications for diseases of the nervous system. *Nat Neurosci* 5:1131–1136
9. Duenker N (2005) Transforming growth factor-beta (TGF-beta) and programmed cell death in the vertebrate retina. *Int Rev Cytol* 245:17–43
10. Hoshino M, Nakamura S, Mori K, Kawachi T, Terao M, Nishimura YV, Fukuda A, Fuse T, Matsuo N, Sone M, Watanabe M, Bito H, Terashima T, Wright CV, Kawaguchi Y, Nakao K, Nabeshima Y (2005) Ptf1a, a bHLH transcriptional gene, defines GABAergic neuronal fates in cerebellum. *Neuron* 47:201–213

Programmed Cell Death

Definition

Cell death by design, in which the cell uses specialized cellular machinery to kill itself. Programmed cell death is a process essential to cell termination, homeostasis, and development. This process allows metazoans to control cell number and eliminate surplus or erroneous cells.

early postural instability, severe axial rigidity, absence of tremor, and poor response to dopaminergic therapy. supranuclear gaze palsy, especially of downgaze, is the defining characteristic. Blepharospasm and eyelid opening apraxia are also common.

► **Parkinsonism**

Progressive Bulbar Palsy

Definition

► **Motoneuron** disease of the ► **brainstem** (*bulb* stands for ► **medulla oblongata** and *palsy* for weakness) with dysarthria (difficulty articulating) and dysphagia (difficulty swallowing).

Pro-inflammatory Cytokines

Definition

Pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α , are overexpressed at the lesion site for several hours to days after central nervous system (CNS) injury. The cells of origin of these cytokines are neurons, astrocytes, microglial cells, infiltrated macrophages, and neutrophils. They are involved in the secondary tissue damage that is produced through a series of autodestructive events (e.g., apoptosis) initiated by the primary trauma. Low concentrations of pro-inflammatory cytokines can be beneficial; however, high concentrations mediate cell death and widespread tissue disruption. Thus, manipulation of this inflammatory response is one of the major therapeutic approaches for CNS injury.

► **Transplantation of Neural Stem Cells for Spinal Cord Regeneration**

► **Tumor Necrosis Factor- α (TNF- α)**

Progressive Multifocal Leukoencephalopathy

Definition

Infrequent disorder of the nervous system that primarily affects individuals with suppressed immune systems (including, allograft recipients such as kidney transplant patients; patients with cancers such as leukemia or lymphoma; and nearly 10% of patients with ► **acquired immune deficiency syndrome (AIDS)**). The disorder, which is caused by a common human polyomavirus, JC virus, is characterized by ► **demyelination** or destruction of the ► **myelin** sheath that covers nerve fibers.

► **Acquired Immune Deficiency Syndrome (AIDS)**

Pro-inflammatory Mediators

► **Central Nervous System Disease – Natural Neuro-protective Agents as Therapeutics**

Progressive Supranuclear Palsy

Definition

Progressive degenerative disease belonging to the family of tauopathies with widespread pathology involving cortical and subcortical structures. In Progressive supranuclear palsy, oculomotor disturbance, early postural instability with falls, and frontal dementia predominate. There is symmetric onset of parkinsonism,

Projection Neurons

Definition

Neurons that send (“project”) their main axon outside a morphologically defined area or nucleus in which their cell bodies are located. The length of the axon depends on the distance between the structures they connect.

Thus, in the cerebral cortex, association axons linking adjacent areas are short compared to corticospinal axons. In the superior colliculus, projection axons to the pretectum are short compared to tectoreticulospinal axons. By opposition, neurons participating exclusively in the intrinsic connections of a given structure are called “local neurons” or “interneurons.”

► **Modulatory Projection Neurons**

Projections

Definition

Axonal extensions, ranging from short to very long, that possess chemical synapses allowing for the electrochemical communication of neurons with other neurons over distance. A neuron with an axon possessing a chemical synapse in relation to another neuron at some distance is said to project to that neuron.

Axons carrying impulses away from a structure comprise efferent projections. Axons carrying impulses into a structure comprise afferent projections.

Prokineticin 2

Definition

A 102 amino acid polypeptide that may function as an output molecule from the suprachiasmatic nucleus (SCN) in transmitting timing behavioral circadian rhythms. It may also function locally within the SCN to synchronize cellular clocks. Receptors for PK2 (PKR2) are abundantly expressed in major target nuclei of the SCN output pathway. Intracerebroventricular infusion of PK2 at night, when endogenous PK2 mRNA levels are low, markedly reduces the nocturnal increase in locomotion.

Mice with a disruption of the PK2 gene display significantly reduced rhythmicity for a variety of circadian physiological and behavioral parameters including sleep-wake cycle, locomotor activity, body temperature, and circulating glucocorticoid as well as glucose levels.

- **Circadian Rhythm**
- **Clock Coupling Factors**
- **Locomotion**
- **Sleep-wake Cycle**
- **Suprachiasmatic Nucleus**

Proliferation

Definition

Production of new daughter cells by cell division.

► **Neural Development**

Promoter

JULIA KIM, DAVID H. FARB, SHELLEY J. RUSSEK
Laboratory of Molecular Neurobiology, Department of Pharmacology and Experimental Therapeutics, Boston, MA, USA

Definition

A promoter contains all the gene regulatory information that is necessary for the expression of its protein product in vivo. The DNA sequence of the promoter can be contiguous lying upstream of the transcriptional start site or it can be separated by large distances dependent upon the presence or absence of key regulatory elements, such as enhancers or silencers, in introns and exons.

The binding of transcription factors to the sequence(s) of the promoter are believed to alter DNA conformation in such a manner that stabilizes the binding of RNA polymerase to enable regulated transcription. A promoter can also be regulated at the epigenetic level through the recruitment of chromatin modulators such as HAT, HDAC, mSin3A, and Swi/snf, that control the accessibility of transcription factors to DNA elements. Cell- and developmental-specific expression often relies on the presence of promoter elements, such as enhancers or silencers, that are located at a distance from the start site in exons, introns, or intergenic regions.

Characteristics Structure

Core: Core promoters are the minimal elements needed for RNA polymerase II to initiate transcription at basal levels using a particular ► [transcriptional start site \(TSS\)](#). The most well-known core promoter region contains a TATA box, around 35 bp upstream of the TSS, and an Initiator element (Inr) that contains the TSS. Not all core promoter regions contain TATA boxes. In fact, many of the regulated genes in the human genome are TATA-less. TATA-less core regions often contain other elements such as the GC box or a binding site for a strong activator protein such as Specificity Protein 1 (SP1). Diversity in core promoter

regions is just beginning to be identified suggesting that this region of the gene is highly specialized and plays an important role in the regulated nature of gene transcription.

Proximal Region: Proximal promoter region contains the Core and around 500 bp of sequence upstream of the ▶TSS. They contain upstream binding sites for activators that are necessary to increase transcription above basal levels.

Distal Region: Distal promoter region is upstream of the Proximal and in most cases contains the recognition sites for activators and repressors responsible for full transcriptional activation, consistent with the levels of gene expression *in vivo*. The Distal region usually contains a few kilobase pairs of DNA lying upstream of the Proximal promoter region that contains the core.

Cis-acting elements and trans-acting factors: A particular set of regulatory sequences that are found within the promoter of a gene are referred to as cis-acting elements. The proteins that bind to these elements, as well as to related elements in multiple genes, are referred to as trans-acting factors, also known as transcription factors.

Gene clusters: A set of two or more genes that are derived from a common ancestor and are functionally related, or encode related gene products, are often found in gene clusters on a particular chromosome. For example, subunit genes coding for the major inhibitory neurotransmitter receptor, type A γ aminobutyric acid (GABA, GABA_AR) are organized as β - α - α - γ or β - α - γ on four human chromosomes [1]. This unique genomic structure suggests that there may be regulatory elements shared by the promoter regions or a single locus of control (as seen for the β -globin genes) that has been preserved throughout evolution.

Alternative Promoters: Many genes use more than one promoter to control either development or cell specific expression. The transcripts produced from these promoter regions increase the diversity of protein products or the stability of their mRNAs. The alternative promoters can be located in a downstream intron or in a distant region upstream from the dominant ▶TSS.

Examples of Promoters, Their Elements and Transcription Factors Studied in the Brain

• Neural Specific Genes

GABRB1 [2] – A gene that codes for the beta 1 subunit of the GABA_AR, the major inhibitory receptor in the nervous system that contains an integral chloride ion channel gated by GABA. GABRB1 is organized in a head-to-head orientation with the $\alpha 4$ subunit gene (GABRA4). The human GABRB1 promoter lacks a ▶TATA-box and contains an Inr element that by itself can determine the cell specific expression of the gene and its autologous regulation by GABA.

GLUR2 [3] – GLUR2 has multiple ▶TSSs that are development and cell-specific. None of the TSSs identified contain TATA boxes and their transcription is modulated by Sp1, within a methylated CpG island, and a GLUR2 silencer that shares 71% similarity to the restrictive silencing factor REST/NRSF (see below).

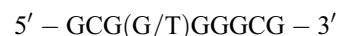
GABBR1 [4] – A gene that codes for the R1 subunit of the GABA_BR, the G-protein coupled receptor that is activated by GABA. Use of alternative promoters, rather than alternative splicing as previously speculated, contributes to the generation of isoforms for the GABA_BR1 subunit. GABA_BR1a expression is marked in the fetal brain and may regulate the formation of presynaptic GABA_B receptors while it is modest in the adult brain. GABABR1 expression is low during development and marked in the adult where it may regulate the formation of postsynaptic GABA_B receptors. The promoter regions of both isoforms are TATA-less and contain functional DNA sequence elements for regulation by the cAMP regulatory binding protein (▶CREB).

Neuropeptide Y (NPY) [5] – NPY is the most abundant neuropeptide in the brain and is expressed in a wide variety of cell populations of the nervous system. Its promoter region contains the partial consensus sequence for transcription factors such as SP1, Activator Protein 1 (AP1) and CAAT box. However, CT-rich, instead of GC-rich, sequences are used by Sp1 to promote transcription.

• A signal-induced transcription factor

Early growth response gene (Egr) and Egr response element (ERE) [6,7]: While the most well known signal activated transcription factor in the nervous system is the ubiquitously expressed CREB, there is a family of immediate early gene (IEG) products known as Egrs that are increasingly being identified in the dynamics of brain function. Egrs bind to the consensus motif (depicted below) in response to signals elicited by neurotransmitters, altering the expression level of certain genes that contain a GC-rich ERE in their promoter region. Egrs link a short-term change in neurotransmission to a functional change via the synthesis of new proteins.

ERE consensus sequence



Egrs are implicated in the transcriptional control of multiple genes via their zinc-finger motif located in the C-terminal region. So far, four family members have been identified (Egr1–4). All of them recognize the same ERE sequence and are homologous, although different spatial and temporal expression is observed. Of the four members, Egr1 is the most well defined and its expression is dependant on activation of the N-methyl-D-aspartate receptor (NMDAR) and mitogen activated protein kinase (MAPK) signaling. However,

the target or the specific mechanisms controlling transcriptional regulation of the other Egr family members is not completely known. Egr3 has recently been identified as a seizure-induced protein controlled by brain derived neurotrophic factor (BDNF, see below) and it plays an important role in learning and memory. Multiple forms of Egr3 that differ in their N-terminus have been described and are being investigated.

- A major target gene for Egr 1 and 3

Activity-regulated cytoskeleton-associated (Arc) protein [8] – A putative target of Egr1 and Egr3 transcription factors, Arc expression is upregulated by robust synaptic activity, such as observed in kainic-acid induced seizures or exploration of a novel environment by rodents. Egrs bind to the ERE site in the Arc promoter. Similar to Egrs, Arc expression is dependant on NMDAR activation and MAPK signaling, highlighting its association with long-term potentiation (LTP) and learning and memory.

- Repressor factor involved in neural specific gene expression

Neuron-Restrictive Silencer Element (NRSE) and Neuron-Restrictive Silencer Factor/RE1 Silencing Transcription factor (NRSF/ REST) [9] – Neuronal specificity can be conferred via unique transcriptional activators or via repressors that silence transcription in non-neuronal cells. Identification of the silencer element NRSE is one of the most important accomplishments in neural specific gene regulation today and its importance to brain function as well as disease is accumulating in the literature. NRSE is found primarily in non-coding sequence and is evolutionarily conserved. NRSEs are found in neuronal genes coding for proteins such as the Na⁺ channel, Synapsin I, BDNF, NMDAR, nAChR, GABAAR, and Neurofilament M, and in non-neuronal genes coding for proteins such as Keratin, human/bovine P450–11β, and skeletal actin. NRSF binds to a 21-nucleotide sequence called the neuron-restrictive silencer element (NRSE/RE1).

NRSE consensus sequence

5' – ttCAGCACCaAGGAcAGcgC – 3'

Uppercase letters: conserved Lowercase letters: less conserved

Although it was initially believed that NRSE containing genes are silenced only in non-neuronal cells via the binding of NRSF, more recent studies have revealed that they also bind to genes within neurons. NRSF contains a zinc-finger DNA-binding domain and interacts with the co-repressors CoREST and mSin3a via two repressor domains found at each end. Once bound to NRSF, the co-repressors recruit histone modifying proteins such as Histone Deacetylase (HDAC) and Methyl CpG binding protein 2 (MeCP2), altering

conformation of the ►chromatin to a transcriptionally silent form (heterochromatin).

NRSF expression in neuronal cells decreases as they become more differentiated and its gene targets are involved in neuronal function, such as ion channels, neurotransmitter receptors, neurotransmitter-synthesizing enzymes, neuronal cytoskeleton, neuropeptides and neurotrophic factors. A truncated splice variant of NRSF, REST 4, has been shown to bind to NRSE rather weakly in neurons and is also found at high levels in biopsies of Small Cell Lung Carcinoma patients.

- A ubiquitous transcription factor with important brain function

Sp1 [10] – Sp1 is a transcription factor that regulates the expression of genes throughout the body. Particular to the brain, it regulates expression of the acetylcholine receptor (AChR) and Huntingtin (Htt). Sp1 is known to bind specifically to GC-rich DNA elements via its zinc-finger motif. With its strong glutamine-rich activation domain, Sp1 recruits basal transcription factor TFIID to DNA and induces marked transcription. TFIID contains TATA box binding protein (TBP) and TBP-associated factors (TAFs) of variable sizes. Of these TAFs, human TAFII130 is of particular interest due to its specific interaction with Sp1. Both Sp1 and TAFII130 bind to the mutant form of Htt, an association that is implicated in Huntington's Disease.

- Activity dependent neural specific signaling molecule

BDNF [11] – There are five exons in the rat BDNF gene and exon I through IV contain promoters that are upstream of one another (designated promoters I-IV). Use of alternative promoters ensures specificity and diversity of gene regulation. For example, BDNF transcription via promoter I is activated after Ca²⁺ influx through L-type voltage-dependent Ca²⁺ channels (L-VDCC), whereas promoter III is activated when Ca²⁺ influx occurs through the NMDAR. The activation of both promoters occurs via binding of phosphorylated ►CREB.

Techniques Used to Study Promoters

Electrophoretic Mobility Shift Assay (EMSA, also referred to as gel shift assay) – EMSA is an in vitro assay used to determine whether a particular transcription factor binds to a known sequence of DNA by identifying if there is specific binding activity in a given nuclear extract when exposed to a particular sequence of DNA or RNA. Extracts of nuclear proteins are incubated with a radiolabeled DNA probe that contains a sequence of interest and the resulting DNA/protein complex is resolved using non-denaturing acrylamide gel electrophoresis. In the absence of extract the probe migrates rapidly towards the bottom, however, in the presence of specific binding protein, the probe's migration is slowed in the gel. Competing cold oligonucleotides of various sequences are used to demonstrate

sequence specificity for the binding interaction. In addition, to determine the identify of nuclear proteins, a specific antibody is added to the binding reaction and presence of a “supershift” (because of the increased size of the complex with the antibody attached, the probe will migrate even more slowly) occurs if the epitope of the binding protein is accessible.

Luciferase Reporter Assay – The luciferase reporter assay is especially useful in studying mammalian transcription because the natural expression of the luciferase gene product is restricted to fireflies. In molecular neurobiology, a vector containing the promoter sequence of interest is placed upstream of the luciferase reporter and promoter activity is studied in transfected primary neuronal cultures derived from different embryonic brain regions by assaying for the amount of light production from cleavage of the luciferase substrate luciferin.

Chromatin Immunoprecipitation (ChIP) – ChIP is utilized to examine the *in vivo* binding of a given protein to a specific promoter segment. After DNA is crosslinked to the DNA-binding proteins, the genomic DNA is sheared into small fragments of 300 bp or less and immunoprecipitated with a specific antibody that recognizes the protein of interest. Upon reverse-crosslinking, detection of the resulting precipitated DNA fragments are done using standard polymerase chain reaction (PCR) or quantitated via real-time PCR with taqman probe and primers. This assay is useful for identifying potential endogenous genes regulated by a particular transcription factor.

Disease

Single Nucleotide Polymorphism (SNP) within the promoter region. Single Nucleotide Polymorphism is characterized as a genetic deviation or change in DNA of more than 1% of a population. Generally, SNPs do not result in any phenotypic changes. However, when the SNPs occur within a coding region or a promoter of a gene, consequences such as a differential response to a drug or an increased predisposition to certain diseases have been observed.

Brain-derived Neurotrophic factor (BDNF). In particular, a genetic variance in the BDNF promoter I was recently identified. This novel variation has a cytosine replaced by adenine at 281 bp upstream of the TSS and causes reduced DNA binding by factors yet to be identified. In addition, this “A” allele decreases BDNF promoter activity in rat hippocampal neurons and an association of the allele with a decrease in psychopathology is reported in a phenotype-genotype analysis using human samples.

Neuropeptide Y (NPY). Lowered activity of NPY has been implicated in the pathophysiology of Schizophrenia. A novel polymorphism within the Japanese population at -485T>C in the promoter region of the NPY gene has been reported in patients suffering from

Schizophrenia. The -485 nucleotide is contained within the Sp1 consensus site and abolishes potential binding site detection.

References

1. Russek SJ (1999) Evolution of GABA(A) receptor diversity in the human genome. *Gene* 227(2):213–222
2. Steiger JL, Russek SJ (2004) GABA-A receptors: building the bridge between subunit mRNAs, their promoters, and cognate transcription factors. *Pharmacol Ther* 101(3):259–281
3. Myers SJ, Peters J, Huang Y, Comer MB, Barthel F, Dingledine R (1998) Transcriptional regulation of the GluR2 gene: neural-specific expression, multiple promoters, and regulatory elements. *J Neurosci* 18(17):6723–6739
4. Steiger JL, Bandyopadhyay S, Farb DH, Russek SJ (2004) cAMP response element-binding protein, activating transcription factor-4, and upstream stimulatory factor differentially control hippocampal GABABR1a and GABABR1b subunit gene expression through alternative promoters. *J Neurosci* 24(27):6115–6126
5. Minth CD, Dixon JE (1990) Expression of the human neuropeptide Y gene. *J Biol Chem* 265(22):12933–12939
6. Beckmann A, Wilce P (1997) Egr transcription factors in the nervous system. *Neurochem Int* 31(4):477–510
7. Li L, Carter J, Gao X, Whitehead J, Tourtellotte WG (2005) The neuroplasticity-associated Arc gene is a direct transcriptional target of early growth response (Egr) transcription factors. *Mol Cell Biol* 25(23):10286–10300
8. Ooi L, Wood IC (2007) Chromatin crosstalk in development and disease: lessons from REST. *Nat Rev Genet* 8(7):544–554 (Review)
9. Dunah AW, Jeong H, Griffin A, Kim YM, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N, Kraine D (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington’s disease. *Science* 296(5576):2238–2243
10. Tabuchi A, Nakaoka R, Amano K, Yukimine M, Andoh T, Kuraishi Y, Tsuda M (2000) Differential activation of brain-derived neurotrophic factor gene promoters I and III by Ca²⁺ signals evoked via L-type voltage-dependent and N-methyl-D-aspartate receptor Ca²⁺ channels. *J Biol Chem* 275(23):17269–17275

Property

VOLKER GADENNE

Department of Philosophy and Theory of Science,
Johannes-Kepler-University, Linz, Germany

Definition

Properties are ways things are; they are features, attributes, traits, characteristics or aspects.

Description of the Theory

Property and Object

Suppose that Jack is bald. Jack belongs to the category of *things* (or *objects*, including persons). Baldness, by contrast, is a *property*. Jack has this property and many other individuals possess it too. Things are bearers of properties and different objects may share the very same property. Things are also said to *exemplify* or *instantiate* properties.

But things are not the only entities that possess properties. Properties can themselves have properties and so can events. “Bald” is exemplified by individual persons and has itself the property of being physical. “Bold” and “shy” are properties of persons too, they are however mental. An event, like having a toothache, may have the property of being short or of occurring after breakfast.

When philosophers speak of objects and properties, they use these concepts in a wide sense. The category of objects may include tables, trees and persons, but also electrical fields or points in space-time. As to properties, many of them are denoted by adjectives, like “green” or “round”. But there are also properties denoted by rather complex predicates. For example, a neuron instantiates (at certain times) a special property denoted by the term “resting potential.” A person may be ascribed the property of being in pain, of believing that snow is white or of wanting to study philosophy. In such cases a person can also be said to be in the *state* of being in pain or in the *state* of believing that snow is white [1].

Ontological Status of Properties

The ontological status of properties has been discussed since Plato [2,3]. *Realists* (in a specific sense of the term) believe that words like “white” or “horse” name the [►universals](#) “whiteness” and “horseness.” Unlike particulars, universals are abstract entities ([►abstract entity](#)). They belong to the real ([►Realism \(as an ontological position\)](#)) world though they are not located in space and time. Some realists (Platonists) think a universal can exist even if it has no instances. Others (following Aristotle) assume that for a universal to exist it has to be exemplified by at least one individual thing.

According to [►nominalism](#), abstract entities do not exist at all. There are only particulars (and perhaps classes of particulars), like individual white things or individual horses. Different things are said to have the same property or belong to the same sort or kind, if the same predicate applies to, or *is true of*, these different things. (Exchange “predicate” with “concept” to get concept nominalism.) Realists object that for a predicate to be true of a particular (or a particular to fall under a concept), that particular must be connected with some real [►entity](#) to which the predicate (or concept) refers. Otherwise the ascription of predicates to particulars

would be an arbitrary matter. The nominalists’ standard reply is that predicates do not function like names (see for the controversy between realists and nominalists [4,5]).

Some philosophers believe there are *essential* and *accidental* properties. A property F is said to be essential to an entity a, if a could not exist without exemplifying F. For example, the number two has essentially the property of being even. It is hard to see how it could lack that property and still be the number two. With respect to concrete objects, it is more difficult to decide whether a property is essential or accidental. It seems that Jack is essentially a human being. In contrast, his property of being a philosopher is accidental, since he could instead have become a postman. In [►possible world semantics](#), the idea of an essential property is expressed as follows; a has the property F essentially if and only if a has F in every [►possible world](#) [6]. For a critique of [►essentialism](#), see [7].

Property and Predicate

If properties are regarded as parts of the real world, they must be distinguished from predicates. Properties are designated by predicates. In the sentence “Jack is bald,” the word “Jack” denotes an individual and the predicate “is bald” refers to a property. Unlike names and predicates, properties are not linguistic entities but real features of the world (an assumption not shared by austere nominalists). It is less clear whether properties are different from concepts (meanings of words). They are different if properties are taken as real and concepts as something in the minds of persons (or as something existing in dependence on minds). However, properties may come close to concepts, if concepts too are conceived as mind independent entities or if both properties and concepts are conceived as mind dependent.

Intrinsic and Extrinsic (Relational) Properties

Objects possess some of their properties in their own right. For example, an object may be round (spherical) and have a mass of two kilograms and it has these features independently of how other things are. Such features are called *intrinsic* properties or *qualities*. Other properties are *extrinsic* or *relational* [1]. Socrates is a teacher of Plato and he is married to Xanthippe. These are relational properties of Socrates, since he has them not independently of other things. (According to some philosophers there are no relational properties; they regard properties and relations as ontologically different, and categorize both as attributes.) Though intrinsic properties are not themselves relational, their specification or measurement usually involves relations between objects. Consider for example how mass (an intrinsic property) is specified. To say that this rod has a

mass of two kilograms is to say that it would balance, on an equal arm balance, two objects each of which balances the standard kilogram.

Dispositional Properties, Causal Powers, and Functional Properties

Special kinds of relational properties are *dispositional properties* and *causal powers*. This billiard ball has the qualities (intrinsic properties) of being spherical and solid. In virtue of these qualities, it has the disposition to roll when placed on an inclined surface. Other dispositional properties are solubility in water or fragility. Having a special disposition is to produce certain behavior under certain conditions. It seems that dispositions are always grounded in non-dispositional properties. For example, being fragile is grounded in a particular molecular structure. An object is fragile in virtue of having that molecular structure. If an object has the dispositional property G in virtue of the non-dispositional (intrinsic, qualitative) property F, F is called a *first-order property* and G a *second-order property*.

Another special kind of relational properties are *functional properties*. Many things are defined by functional descriptions, for example, a knife, a clock or an eye. An object has the property of being a clock, not because of the material of which it is made, but because it satisfies a certain job description – it keeps time. Similarly, an eye can be made of different materials and take different forms (compare our eye to that of the horse or the honeybee). What makes it an eye is a special functional property or functional role – it extracts information from light radiation and makes that information available to the system it subserves. Functional roles can best be described with the help of causal relations. Therefore, philosophers often speak of “causal roles” instead of functional roles.

Mental Properties

A major problem in the philosophy of mind is the status of mental properties. Physicalists have tried to demonstrate that the mental is nothing over and beyond the physical organism and its physical/biological properties. This view includes the theory that all mental properties are realized as physical/biological properties; according to advocates of reductionist physicalism, mental properties are even reducible to physical/biological properties. Similarly, functionalists have held that mental properties can be understood as functional properties (which are themselves realized as physical properties). Consider for example the property of being in pain. According to functionalism, roughly speaking a mental state is a pain if it is caused by specific stimuli (e.g. tissue damage), gives rise to specific thoughts and wants (e.g. about how to end the unpleasant state) and causes specific behavior (e.g. withdrawal).

It has been objected against physicalism and functionalism that they could not adequately account for *phenomenal qualities* or ► **qualia** (singular: **quale**). Some mental states, especially, sensations and feelings, are characterized by specific phenomenal qualities. Think of the painful, hurting character of a sharp headache. Such phenomenal qualities seem to be intrinsic properties not extrinsic (relational) ones. It is hard to see how phenomenal qualities could be identified with or reduced to physical properties, causal powers or functional roles. But if they cannot be reduced to the physical domain, it seems difficult to understand how they can have any effect on the physical organism and its behavior. The status of mental properties, especially phenomenal ones, is still controversially discussed.

References

1. Kim J (1996) *Philosophy of mind*. Westview, Boulder
2. Plato (1961) *Parmenides*. In: Hamilton E, Cairns H (eds) *Plato: the collected works*. Pantheon Books, New York
3. Mellor DH, Oliver A (eds) (1997) *Properties*. Oxford University Press, Oxford
4. Armstrong DM (1989) *Universals*. Westview, Boulder
5. Loux MJ (1998) *Metaphysics*. Routledge, London
6. Kripke SA (1980) *Naming and necessity*. Harvard University Press, Cambridge
7. Grossmann R (1983) *The categorical structure of the world*. Indiana University Press, Bloomington

Proposition, Propositional Attitudes

Definition

A proposition is what is asserted as the result of uttering a sentence; propositions are considered to be the meanings of closed sentences (as opposed to open sentences or predicates), and they are considered to be the bearers of truth and falsity. Propositions are expressed by that-clauses (the sentence “Hannah laughs,” for instance, expresses the proposition (means) that Hannah laughs) and can be thought of as pairs consisting of objects and properties (like <Hannah; laughs>) or relations (like <<Hannah, Fred>; is taller than>).

A subject S can have different mental postures towards a proposition P, for example believing, remembering, desiring, intending, fearing, hoping etc.

In that case, S has a propositional attitude. A propositional attitude is an intentional relation R between a subject S and a proposition P, such that S bears R to P. Propositional attitude ascriptions are made

up of a name for some thing, like “Fred,” followed by a name for an attitude, like “believes,” followed by an expression for a proposition, like “that Hannah laughs.”

- [Epiphenomenalism](#)
- [Possible World](#)

Propositional Knowledge

Definition

Propositional knowledge is the kind of knowledge one can communicate using some proposition, i.e. in English using some phrase of the form “that p” where “p” can be replaced by some complete declarative sentence.

- [Knowledge](#)

Proprioception

SIMON GANDEVIA

Prince of Wales Medical Research Institute, Sydney, NSW, Australia

Introduction

The production of ► [voluntary movements](#) usually occurs effortlessly with few errors. We rarely drop objects held in the hand or fall while walking. This requires coordinated activity involving cognitive, sensory and motor areas of the cerebral cortex. Ultimately the correct output is generated by ► [motorneurons](#) in the ► [spinal cord](#) and ► [brainstem](#) which then produce the correct changes in force and length of muscles. For muscles to exert continuously the proper forces on the skeleton requires the brain to plan, initiate and control movements. A set of sensory processes underlies this ability. It is variously termed “proprioception” or “► [kinaesthesia](#).” These terms are now often used interchangeably, although proprioception is broader in its scope.

Proprioception and kinaesthesia refer to a class of sensations or sensory-motor processes which include the ability to detect movement and position at different joints and the ability to judge forces exerted by muscles

and the heaviness of objects they lift. Knowledge about the timing of muscle contractions and knowledge about the overall body image are now also covered by these umbrella terms. Deficits that impair proprioception impair the control of voluntary movement and posture, whereas diseases that impair movement and posture usually have deficits in some aspects of proprioception. This synopsis focuses on the sensations of joint position and movement although some other areas are briefly mentioned.

The neural mechanisms underlying proprioception have been hotly debated for more than a century [1]. Much of this controversy has arisen because experimentalists and clinicians have taken a narrow view of what proprioception encompasses. In contrast, theoreticians have proposed complex models of how proprioception might contribute to movement control, but these have been difficult to validate.

On the “input” side, groups of specialized sensory receptors in the skin, joint and muscles respond to mechanical strains and signal the state of the limb to the spinal cord and brain. Evidence of the contribution of each of these receptor groups is summarized below. For these signals to be transformed into useful sensations which can be reported verbally requires central processing so that the different input signals are calibrated to the Newtonian state of the body, and combined or amalgamated to provide a body map (or “representation”) which can help guide movement (see also ► [Phantom limb sensation and pain](#)).

Because a particular proprioceptive state (e.g., the angle of a joint) can arise under passive conditions with muscles relaxed, or active conditions with muscles contracting, most proprioceptive models also include an input from motor command signals. Peripheral signals provide feedback that is evaluated against what movement has been commanded and what proprioceptive state might be expected. Various terms for these command signals have been coined including an ► [efference copy](#) or ► [corollary discharge](#). A requirement for such signals is not unique to evaluation of proprioceptive signals, but is equally necessary in other modalities such as cutaneous, visual and ► [vestibular sensation](#), in which changes in the peripheral signals can be produced by self-generated forces or externally-generated events. An interesting example occurs when a tickling skin sensation is felt when generated externally but not when the same stimulus is self-generated [2].

Peripheral Proprioceptive Signals

There are two steps in the establishment of a proprioceptive role for a particular class of sensory receptors. First, the receptors must encode variables such as the forces exerted by muscles or changes in joint angles in their discharge. Second, the discharge must be capable of producing a change in perception of that

proprioceptive variable. The first step is achieved by recording the discharge of the receptors. The second requires that changes in the discharge evoke changes in sensation. This can be achieved by finding a proprioceptive illusion when the receptors are activated selectively. Alternatively, performance in a proprioceptive test may diminish when the receptors are eliminated, such as when a diseased or damaged joint is replaced by an artificial one.

Of the peripheral proprioceptive signals, those arising in specialized muscle receptors are considered the most important [1,3,4] (see ►[Proprioception: Roles of Muscle Receptors](#), and ►[Movement Sense](#)). ►[Muscle spindle](#) endings can be activated by local length changes and their firing can also be modified by a specialized ►[fusimotor system](#) that can modulate the background firing rate and gain of the endings. The ►[primary muscle spindle endings](#) are exquisitely responsive to muscle length changes including vibration. When a muscle (or its tendon) is vibrated at ~100 Hz, subjects experience an illusion consistent with the muscle lengthening, but also occupying a more lengthened position [5]. When the vibration is adjusted so that secondary spindle endings are more effectively activated, the illusion is more one of position than of movement. The central nervous system interprets these unexpected proprioceptive signals according to the current body map (see ►[Phantom limb sensations and pain](#)), and this leads to errors in voluntary movements and posture [6]. Muscles also contain specialized receptors (►[Golgi tendon organs](#)) which encode the active forces generated by voluntary contraction. These signals probably contribute to sensation of muscle force.

Until recently, specialized receptors in the skin were not considered to have a role in proprioceptive sensations, although it had long been realized that such receptors discharge with movement of nearby joints and that their activity contributed to the reflex control of movement in activities such as walking and grasping. Some populations of ►[cutaneous receptor](#) encode the pattern of local skin strain and its change with changes in joint position [7], while others encode the timing of voluntary movement and any disturbances to it (see ►[Proprioception: Role of cutaneous receptors](#)). Stretch receptors in the skin (probably innervating ►[Ruffini endings](#)) discharge when the skin around a joint is stretched by moving it via threads attached to tape stuck to the skin. Subjects then commonly report that the underlying joints are moving in a direction consistent with the pattern of artificial skin strain. These illusory sensations of movement are amplified when combined with muscle spindle signals evoked in appropriate muscle spindle ending populations by tendon vibration. Illusions evoked by skin stretch can be evoked at joints in the hand as well as at large proximal joints such as the

elbow and knee [8]. Insight into the predictive capacity of the cortical proprioceptive decoders comes from observing that when skin and muscle receptors are activated artificially to produce proprioceptive illusions, subjects may report completely impossible anatomical positions. To the subject of the illusion, this extraordinary disruption of reality seems completely natural. Supportive evidence for the proprioceptive role of non-muscle, presumably skin receptors, derived from studies of the hand when nerves innervating the fingers (but not their muscles) have been anaesthetized [9].

Throughout most of the last century, joint receptors were considered so influential in proprioception that the term “►[joint position sense](#)” was adopted by clinicians in the belief that such receptors were crucial contributors. Evidence for the belief was much weaker than admitted. Specialized slowly adapting receptors in joint capsules and ligaments usually discharge only at one (or more) extreme of the usual physiological range of joint movement, or they discharge when abnormal stresses are put upon a joint [10]. Relatively few receptors discharge progressively across the movement range in a way that allows them to signal the angular motion (see ►[Proprioception: Role of joint receptors](#)). Electrical stimulation of digital nerves or single joint receptors can evoke illusory sensations of joint distortions and movement [11,12]. The difficulty of selectively activating a natural population of these receptors precludes a quantitative assessment of their role. Intra-articular anesthesia or joint replacement does not produce major deficits in proprioceptive sensation, which may simply indicate the redundancy in afferent sources of information (see ►[Proprioception and orthopedics](#)).

Motor Commands and Central Processing

In the planning and execution of movement, signals related to the voluntary command are generated. These signals have a number of roles to play in the control of movement and posture [13], but exactly how this is achieved for limb movement is uncertain. Lessons from robotics and engineering, as well as studies in insects and fish, reveal that access to command signals for movement control through predictive modeling of their action on the body, and through monitoring of their outcome via feedback is likely to be important in control of human movement and posture [14].

The oculomotor system is one example where central command signals help ensure the perceptual stability of our visual world. A second example is found in the judgment of exerted force and the heaviness of objects lifted by muscle contraction. Here, signals related to the size of the outgoing command bias the judgments. As a result, we are familiar with the increase in apparent heaviness of objects we lift when muscles become fatigued [15]. This type of perceptual illusion

has been rigorously investigated under many circumstances affecting the relationship between the motor command required and the actual muscle force achieved, and the maxim holds that objects appear heavy wherever the efficiency of the neuromuscular apparatus is impaired [3]. However, the perceived force is not a simple readout of the motor command delivered (nor of the motor cortex output), because this readout must be interpreted in the light of ongoing afferent signals.

Experimental studies have usually focused on the role of command-related signals in highly volitional tasks requiring, or triggered by, an external cue. In activities such as walking in which the contractions occur more automatically, the access and processing of command signals may differ. Thus, the voluntary effort required to generate the force that can lift you onto the ball of one foot exceeds that during walking when similar forces are required. An additional complication that has not been resolved is how the muscle spindle signals from voluntarily contracting muscles are interpreted, because their signal is a resultant of the local strain on the receptor induced by the environment and that induced by the fusimotor system. This independent motor supply to muscles can alter the gain and set point of the spindle's response [16]. One way to resolve this complication is the reliance on several afferent sources of input (from the skin, joints and non-contracting muscles) rather than a signal arising solely in the active muscles.

It had long been thought that motor commands did not play a major role in sensing the position and movement of joints. However, recent work with normal subjects in whom a phantom hand has been induced by deafferentation and paralysis challenges this view. The phantom hand moves in the direction in which it is willed to move, and the size of the movement increases with the level of motor command and effort [17]. Hence, the isolated command to move, in the absence of any input from proprioceptors, generates an illusion. If this applies, as seems likely, when there are normal sensory signals, it will be clear that this group of proprioceptive sensations, like force-related sensations, is also biased by the command signals.

Presumably, the brain devises its best estimate of the proprioceptive state based on an amalgam of inputs, some command-related, some originating in different classes of sensory receptors, and some derived from internal predictive models. Visual signals and vestibular signals provide additional frames of reference against which the proprioceptive state of the limbs in extra personal space can be gauged. Vestibular signals extend the proprioceptive system by providing information about the head's position and its movement relative to gravity. Visual signals extend the proprioceptive system

by calibrating it against external objects and in some circumstances visual inputs override proprioceptive ones.

This proprioceptive amalgam can adapt to rapidly changing conditions brought about, for example, by muscle fatigue or by changes in a limb's orientation to gravity occurring acutely with natural movements and posture, and chronically in the microgravity of an orbiting spacecraft (see ►[Proprioception: Effect of gravity](#)). Here, some receptors may act as "load" sensors. Proprioception must also adapt to other changes brought about by musculoskeletal growth, damage and disease, as well as the impairments accompanying ageing (see ►[Proprioception: Effect of ageing](#)). In the elderly, reduced proprioception contributes to postural instability and falling.

Studies using non-invasive imaging of the human brain have revealed that proprioceptive inputs from muscle receptors have specific projections to major cortical areas, particularly the primary motor cortex and its adjacent area (area 3a in the so-called "somatosensory" cortex). These areas have a direct role in movement production [18] as they contain cells projecting to the spinal cord and even to motoneurons. In addition, some other cortical areas are activated in a less specific way, for example, part of the supplementary motor area is active when either the left or right hand is vibrated to produce illusory movements and part of the cingulate motor area is active when the hand or foot is vibrated on the contralateral side. Other parietal and frontal cortical areas are active in producing the proprioceptive "amalgam" that is integrated with our "body image," with visual circuits, and with cognitive centers.

Conclusions

Proprioception is a broad term encompassing several sensations which are needed for normal movement. It is likely that the brain optimizes the use of both peripheral signals from muscle, skin and joint receptors together with signals about the timing, destination and strength of centrally generated command signals. The proprioceptive system must continually determine what changes in the proprioceptive state are self-induced and what represent changes brought about by external forces. It must also adapt to changes occurring to the musculoskeletal system.

While many of the afferent mechanisms are now well established, the central mechanisms are less well understood. Current studies are using a range of non-invasive methods to extract the location, strength and timing of the responsible neural activity. Further studies will focus on the precise deficits that occur when movement control is disrupted by a range of diseases, from schizophrenia to Parkinson's disease. Although it is clear that central processing in traditional

somatosensory, motor and associative frontal and parietal areas is involved, the way in which cerebellar and basal ganglia circuits contribute is poorly understood.

References

1. McCloskey DI (1978) Kinesthetic sensibility. *Physiol Rev* 58:763–820
2. Blakemore SJ, Wolpert DM, Frith CD (1998) Central cancellation of self-produced tickle sensation. *Nat Neurosci* 1:635–640
3. Gandevia SC (1996) Kinesthesia: roles for afferent signals and motor commands. In: Rowell LB, Shepherd JT (eds) *Handbook on integration of motor, circulatory, respiratory and metabolic control during exercise*, American Physiological Society, Bethesda, pp 128–172
4. Proske U (2006) Kinesthesia: the role of muscle receptors. *Muscle Nerve* 34:545–558
5. Goodwin GM, McCloskey DI, Matthews PB (1972) The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain* 95:705–748
6. DiZio P, Lathan CE, Lackner JR (1993) The role of brachial muscle spindle signals in assignment of visual direction. *J Neurophysiol* 70:1578–1584
7. Edin BB, Abbs JH (1991) Finger movement responses of cutaneous mechanoreceptors in the dorsal skin of the human hand. *J Neurophysiol* 65:657–670
8. Collins DF, Refshauge KM, Todd G, Gandevia SC (2005) Cutaneous receptors contribute to kinesthesia at the index finger, elbow, and knee. *J Neurophysiol* 94:1699–1706
9. Gandevia SC, McCloskey DI (1976) Joint sense, muscle sense, and their combination as position sense, measured at the distal interphalangeal joint of the middle finger. *J Physiol* 260:387–407
10. Burke D, Gandevia SC, Macefield G (1988) Responses to passive movement of receptors in joint, skin and muscle of the human hand. *J Physiol* 402:347–361
11. Gandevia SC (1985) Illusory movements produced by electrical stimulation of low-threshold muscle afferents from the hand. *Brain* 108:965–981
12. Macefield G, Gandevia SC, Burke D (1990) Perceptual responses to microstimulation of single afferents innervating joints, muscles and skin of the human hand. *J Physiol* 429:113–129
13. Gandevia SC (1987) Roles for perceived motor commands in motor control. *Trends Neurosci* 10:81–85
14. Frith CD, Blakemore SJ, Wolpert DM (2000) Abnormalities in the awareness and control of action. *Philos Trans R Soc Lond B Biol Sci* 355:1771–1788
15. Gandevia SC, McCloskey DI (1977) Sensations of heaviness. *Brain* 100:345–354
16. Matthews PBC (1981) Evolving views on the internal operation and functional role of the muscle spindle. *J Physiol* 320:1–30
17. Gandevia SC, Smith JL, Crawford M, Proske U, Taylor JL (2006) Motor commands contribute to human position sense. *J Physiol* 571:703–710
18. Naito E, Nakashima T, Kito T, Aramaki Y, Okada T, Sadato N (2007) Human limb-specific and non-limb-specific brain representations during kinesthetic illusory movements of the upper and lower extremities. *Eur J Neurosci* 25:3476–3487

Proprioception and Orthopedics

KATHRYN M. REFSHAUGE

Faculty of Health Sciences, University of Sydney, Sydney, NSW, Australia

Synonyms

Kinesthesia; Movement detection; Position sense; Movement discrimination

Definition

Proprioception refers to the group of sensations related to limb position and movement, muscle force, timing of muscle contractions and posture and size of a body “schema” of one or more joints. Peripheral proprioceptive signals arise from discharge of receptors located in muscle, joints and cutaneous tissue, although there is continuing debate concerning their relative contribution to conscious proprioceptive sensations and the nature of their contribution. Proprioceptive sensations are also derived from centrally generated motor commands and the interaction between the afferent and efferent signals.

Characteristics

Quantitative Description

Each of the proprioceptive sensations requires a different method of testing, with consequent different levels of acuity according to the test method. Acuity varies among joints in a single individual, even when tested with the same method. The only proprioceptive sensation to be systematically measured for human joints in the same individual is the sensation of joint movement, measured using detection levels for perception of passive movement. In both the leg and the arm, proximal joints have better acuity than distal joints when expressed as angular displacement. For example, in the leg, for passive movements imposed at 0.5°/s, movements of ~0.2° can be detected at the hip, ~0.6° at the knee, ~0.5° at the ankle and ~21° at the interphalangeal joint of the big toe. Similarly in the arm, for passive movements imposed at 1°/s, movements of ~0.2° can be detected at the shoulder, ~0.6° at the elbow and ~5° at the distal interphalangeal joint of the finger.

Test conditions can be manipulated to increase or decrease proprioceptive acuity. Small contractions of the muscles around the joint can improve acuity tenfold whereas fatigue increases the error in position matching tasks. Muscle history can also alter acuity. Finally, proprioceptive acuity improves with increasing velocity and decreases with increasing age.

Proprioceptive performance cannot be generalized across the wide variety of tests in common use because there is no relationship between the different tests. Therefore a single test is not adequate to make judgments about

general proprioceptive status in health or after injury. This lack of relationship is likely to account, at least in part, for the conflicting results found for the effect of injury on proprioception.

Higher Level Components

Cortical projections must exist for a role to be assigned to the peripheral receptor discharge measured during movements. Such projections have been established for all proprioceptors.

Lower Level Components

Three classes of afferent contribute to proprioceptive sensibility, including cutaneous, muscle and tendon and joint capsule and ligament afferents. The adequate stimulus for all three is stretch of the tissue in which they are located, although cutaneous and joint receptors also respond to other stimuli. The major debate over the last century has concerned the contribution of each to proprioceptive sensations. It is now clear that all classes contribute to proprioceptive sensations and the debate is now directed at the nature of the contribution. Although it was hypothesized that cutaneous afferents may facilitate muscle afferents, more recent evidence suggests that such facilitation is unlikely. Based on both psychophysical and microneurographic evidence, the contemporary view is that cutaneous input is integrated with that from muscle spindles to provide accurate perception of joint position and movement.

Function

The ability to perceive limb movement and position is essential to normal movement and posture. Without this ability, function is severely disturbed because attempts to move must be guided and monitored using vision. Proprioception underlies all normal movement and its control.

Orthopedic Pathology

Interest in the effect of orthopedic pathology on proprioception has most often been directed at osteoarthritis, joint replacement and ligament injuries and rarely at non-specific conditions such as low back and neck pain. The effect of orthopedic pathology on proprioception varies with the pathology but a proprioceptive deficit has been found consistently in very few conditions. In most orthopedic pathologies, a deficit is not evident, the literature is inconsistent or a deficit has been found in some but not all of the different proprioceptive tests. The more important question concerns the relevance of a deficit and the magnitude of deficit required for it to impact on function.

Osteoarthritis (OA)

Proprioception has been extensively investigated in knees with OA. All studies have consistently found

impairments in both joint position sense and detection of movement compared with healthy controls [1]. The magnitude of the deficit in movement detection was $\sim 1.3^\circ$ (normal $\sim 2.3^\circ$) and in joint position sense $\sim 2.9^\circ$ (normal $\sim 2.6^\circ$). Such a deficit has also been found in the contralateral unaffected knee, with proprioception in both knees being impaired compared with healthy controls [1], leading to speculation that this could indicate central changes. However, no correlation has been found between proprioceptive impairment and severity of disease [1], function or pain. Given the lack of correlation between proprioceptive deficit and function and the small magnitude of the deficit, the consequence of this deficit is unlikely to be functionally relevant.

Total Joint Replacement

It is of particular interest that total joint replacement for knee OA does not necessarily impair proprioception, despite removal of the articular surface. Different studies have found total joint replacement to variously impair, not change or even improve proprioception, although probably not to normal acuity. The magnitude of reported deficits was small, being between 0.3° and 0.72° for threshold to movement detection. However, even when proprioception was found to be impaired after surgery, balance measurements remained normal and clinical outcome was reported as excellent for replaced knees [2], indicating that small proprioceptive impairments do not manifest as functional deficits.

The most common *ligament* injuries involve the anterior cruciate ligament (ACL) at the knee and the lateral ligament complex at the ankle. Proprioception has been extensively investigated in both injuries, motivated by the belief that proprioceptive deficits are associated with persisting disability.

Anterior Cruciate Ligament Rupture

It has been suggested that the ACL has an important proprioceptive role via the fusimotor system and that its loss should therefore cause a significant proprioceptive deficit. However, the evidence does not uniformly support this proposal. A deficit in threshold to movement detection of 1.5° has been found compared with the contralateral uninjured knee and of 0.5° compared with healthy controls [3], but others found no impairment. Furthermore, no impairment was found in joint position sense in ACL deficient knees compared with healthy controls by most authors, although a deficit of up to 4.5° was found by others [4] and the deficit was significantly worse in the mid-range of movement [4]. When both threshold to movement detection and joint position sense were measured in the same subjects, there was no correlation in performance [5], suggesting that a deficit may be specific and that performance on a single proprioceptive test cannot be generalized. However, no study investigated proprioception in

rotation movements, the direction of instability in ACL-deficient knees.

The effect of reconstructive surgery after ACL rupture on proprioception is also unclear. After surgical reconstruction, some authors found that movement detection was restored to normal, others found improved acuity but not to normal levels and unexpectedly, Co et al. [6] found that reconstructed knees were even more accurate than healthy controls by 0.4° . The findings for joint position sense were also inconsistent; reconstruction was variously found to confer no benefit [6] or to improve acuity, but not to normal [3]. These conflicting results potentially arise because not all ACL-deficient knees have a proprioceptive deficit to address. It is tempting to suggest that any improvement is due to the improved stability of the joint, but proprioceptive acuity correlated poorly with mechanical stability [4,3]. Alternatively, improved joint kinematics may normalize input from the muscles, thereby enhancing proprioceptive signals.

Even when proprioceptive deficits were found, they were generally small. Nevertheless the impact on function is uncertain. Although some authors found a high correlation (range, $r = 0.6$ – 0.9) between proprioception and function [4], others failed to find a relationship [3]. It is difficult to explain these conflicting results. It is possible that the different findings relate to different comorbid pathologies included in the studies, such as associated meniscal damage, although again the findings are inconclusive; concomitant meniscal or chondral damage was found to relate to proprioceptive deficits by some but not others [3].

Lateral Ligament Sprain at the Ankle

Persisting symptoms of pain and instability are common after ankle inversion sprain and are frequently attributed to a deficit in proprioception. Impaired movement detection has been found by most authors in the inversion-eversion plane after recurrent sprain compared with healthy controls, the deficit in movement detection being $<1^\circ$ and in some cases $<0.5^\circ$. However, in the plantarflexion-dorsiflexion plane most authors found no impairment [7]. Findings for joint position sense in the inversion-eversion plane are less consistent; a significant impairment was found by some authors but not by others. Joint position sense in the plantarflexion-dorsiflexion plane has yet to be investigated. Consistent with other ligament injuries, there was no correlation between proprioceptive performance and mechanical stability.

These findings suggest that any proprioceptive deficit after ankle inversion sprain is specific to the inversion-eversion plane of movement and to particular proprioceptive tests. The deficit is potentially related to the anatomical structures involved in the sprain, particularly those that resist inversion rather

than plantarflexion forces. Damage to these structures may therefore cause impairment only in proprioceptive tests specific to the inversion-eversion plane of movement.

Therapy

Proprioceptive training is considered an integral part of rehabilitation after many orthopedic injuries to improve assumed deficits and to prevent further injury, despite lack of knowledge about: the magnitude of deficit that is clinically meaningful; whether proprioception can be trained; and, if a deficit does exist and proprioception can be trained, whether improved proprioception is associated with improved function and reduced risk of re-injury.

The magnitude of proprioceptive deficit, when it exists in orthopedic pathology, is small in most test paradigms, generally being within one standard deviation of the average performance of control subjects. Although this difference is statistically significant in some cases, it is unlikely to be functionally relevant, because a deficit has not consistently been associated with pain or loss of function. It is possible, however, that a small deficit may be critical in situations where small errors could have considerable impact on highly skilled performance.

The most common forms of “proprioceptive training” are performance of tasks on an ankle disc or wobble board and agility training. It is indisputable that such training improves motor control; however, whether proprioception is improved is largely unknown. In the two studies that examined the effect of training on joint position sense at the ankle, one found selective improvement of $\geq 0.5^\circ$ in error reduction at some, but not all, test angles [8], while the other found no change with training. There is currently insufficient evidence to conclude that either joint position sense or movement detection can be improved.

The major purpose of “proprioceptive” training, however, is to prevent re-injury. There is no direct evidence of a role for proprioception in prevention of injuries because the relationship between proprioception and injury risk has not been established. The few studies that have investigated the efficacy of “proprioceptive” training for injury prevention, have found the risk to be reduced, although the relationship between proprioception and injury was not investigated. Risk of ACL injury was reduced by 88% by agility training compared with control intervention. The pooled results of Wedderkop et al. [9] and Verhagen et al. [10] show that ankle disc training programs significantly reduced incidence of ankle injury, with an odds ratio for the pooled data of 0.41 (95% CI 0.268–0.629). This reduction in risk of injury has not been correlated with changes in proprioception and proprioception has not been used as an outcome measure.

Conclusions

Taken together, the findings suggest that a proprioceptive deficit has been consistently found for degenerative joint disease, but not for any other pathology and these deficits may be improved, perhaps to normal, by surgical intervention. Selective proprioceptive deficits occur in unstable joints, but the deficit is generally small. The lack of consistent findings may be attributed to the lack of relationship in proprioceptive acuity among different proprioceptive tests and therefore identification of a deficit is likely to depend on the specific proprioceptive test measured.

Given the poor relationship between proprioception and function, the relevance of small proprioceptive deficits is unknown. Potentially these small deficits could impair highly skilled performance, but are unlikely to manifest as functional problems in normal daily activities and therefore may not require remedial therapy.

References

1. Koralewicz LM, Engh GA (2000) Comparison of proprioception in arthritic and age-matched normal knees. *J Bone Joint Surg* 82-A:1582–1588
2. Pap G, Meyer M, Weiler HT, Machner A, Awiszus F (2000) Proprioception after total knee arthroplasty: a comparison with clinical outcome. *Acta Orthop Scand* 71:153–159
3. Reider B, Arcand MA, Lee H et al. (2003) Proprioception of the knee before and after anterior cruciate ligament reconstruction. *Arthroscopy* 19:2–12
4. Fremery R, Lobenhoffer P, Zeichen J, Skutek M, Bosch U, Tscherne H (2000) Proprioception after rehabilitation and reconstruction in knees with deficiency of the anterior cruciate ligament: a prospective, longitudinal study. *J Bone Joint Surg* 82:801–806
5. Friden T, Roberts D, Zatterstrom R, Lindstrand A, Moritz U (1997) Proprioception after an acute knee ligament injury: a longitudinal study on 16 consecutive patients. *J Orthop Res* 15:37–644
6. Co FH, Skinner HB, Cannon WD (1993) Effect of reconstruction of the anterior cruciate ligament on proprioception of the knee and the heel strike transient. *J Orthop Res* 11:696–704
7. Refshauge KM, Kilbreath SL, Raymond J (2003) The effect of recurrent ankle sprain on proprioceptive acuity for inversion-eversion movements. *J Orthop Sports Phys Ther* 33:166–173
8. Eils E, Rosenbaum D (2001) A multi-station proprioceptive exercise program in patients with ankle instability. *Med Sci Sports Exerc* 33:1991–1998
9. Wedderkopp N, Kaltoft M, Lundgaard B et al. (1999) Prevention of injuries in young female players in European team handball: a prospective intervention study. *Scand J Med Sci Sports* 9:41–47
10. Verhagen E, van der Beek A, Twisk J, Bouter L, Bahr R, van Mechelen W (2004) The effect of a proprioceptive balance board training program for the prevention of ankle sprains. *Am J Sports Med* 32:1385–1393

Proprioception: Effect of Aging

STEPHEN R. LORD

Prince of Wales Medical Research Institute and University of New South Wales, Sydney, NSW, Australia

Definition

Proprioception is the discrimination of the positions and movements of body parts based on information other than visual, auditory or verbal. The immediate stimuli come from changes in length and from tension, compression and shear forces arising from the effects of gravity, from the relative movements of body parts and from muscular contraction [1]. Studies assessing proprioceptive age changes have used the terms proprioception, kinaesthesia and joint position sense interchangeably and both passive and active movement paradigms have been used to assess proprioceptive judgments.

Ageing is an orderly or regular transformation with time of representative organisms living in representative environments.

Characteristics

Function

In 1937, Laidlaw and Hamilton [2] were the first researchers to demonstrate an age related decline in proprioception. They measured the ability of 60 subjects to detect movement in the shoulder, elbow, wrist, metacarpophalangeal joints in the upper limb and hip, knee, ankle and first metatarsophalangeal joints in the lower limb. They found that subjects aged 17–35 years had lower thresholds and superior ability to detect direction of joint movements than subjects aged 50–85 years. The hip was the most sensitive joint and the metatarsophalangeal joint was the least sensitive. They also found a wide range in perceived movement threshold and that this variability was most marked in the older age group.

More recent studies and referenced in Lord et al. [3] have, in general, confirmed Laidlaw and Hamilton's findings. Kokmen et al. [3] measured the threshold at which subjects could detect metacarpophalangeal and metatarsophalangeal joint motion. These joints were passively moved in an increasing sinusoidal flexion extension mode (a nonspecific test of joint movement only). They found that there was no difference in metacarpophalangeal joint motion detection between young subjects (aged 19–34 years) and older subjects (aged 61–84 years) at all frequencies between 0.5 and 8 Hz. They did find, however, a significant difference in metatarsophalangeal joint motion detection between young and old subjects at the lowest frequency of 0.5 Hz. At higher frequencies, the older age group

showed higher but insignificant increases in metatarsophalangeal joint motion thresholds. Variability in threshold perception performance increased with age and joint motion thresholds for the metacarpophalangeal joint were significantly smaller than for the metatarsophalangeal joint in the older group at all frequencies except for 8 Hz. No such trend was evident in the young age group, which suggests that joint motion sense may decline more with age in the lower limb compared with the upper limb.

In a recent study, Ferrell et al. [3] used a position-matching task to assess the ability of subjects to detect displacements at the proximal interphalangeal joint of the index finger. These displacements were imposed at an angular velocity of $2^\circ/\text{min}$, which is below the threshold for movement detection. An older group of subjects (mean age = 57 years) showed significantly poorer performance in detecting the position of the index finger than a group of younger subjects (mean age = 24 years). The size of the matching error had correlation of 0.47 with age.

Two studies have examined the effect of age on the joint position sense of the knee. Skinner et al. [3] measured joint position sense of the knee in 29 subjects with normal knee joints ranging in age from 20 to 82 years. Joint position sense was determined by the threshold of detection of an experimenter-induced movement of the knee joint and by the ability to reproduce passive knee positioning. They found that joint position sense as measured by both tests deteriorated significantly with age.

Kaplan et al. [3] used a clinical goniometer to measure the ability of 29 women to match the position of each knee with the other knee and like Skinner et al. to reproduce a knee joint position after a period of rest. They found that an older age group (aged 60–80 years) performed significantly worse than a young group (aged 22–27 years) in both tests. In the experimental paradigm where subjects had to match the position of a knee with the other knee, they found no difference between the number of trials undershot and overshot in the young group, but a tendency to underestimate knee joint angle in the older group. The reported failure of the older group to reproduce the knee joint position may however have resulted from motor deficits as well as proprioceptive deficits.

In a study of 550 women aged 20–99 years Lord et al., there was a decline in proprioception with age as measured with a seated lower limb-matching task [4]. The average error in aligning the great toes either side of a vertical protractor placed between the legs increased from 0.7 degrees (SD = 0.3) in subjects in their twenties to 1.9 degrees (SD = 1.7) in subjects aged 65 plus years. Overall, there was a weak but significant association between error size and age across all age groups, $r = 0.20$.

Three clinical studies have investigated whether there is a decline in proprioception beyond 65 years of age. Howell [3] examined the ability of 200 patients aged 65 years and over to detect joint position sense of the great toes and to touch their noses with their eyes closed. He found that most patients could determine experimenter-induced movements of their toes but that approximately 44% of patients in all age groups above 65 showed abnormalities in the nose touching test. There were no significant changes with age in either test.

MacLennan et al. [5] also examined the ability of 308 elderly persons to identify the position of their great toes after they were manually moved by the experimenter. They found that the prevalence of inability to appreciate changes in position of the toe was significantly greater in the age group 75 years and over than in the age group aged 65–74 years for both males and females. Similarly, Brocklehurst et al. [6] measured the ability of 151 persons aged 65 years and over to detect experimenter-induced movements of the toe and ankle. They found no association between age and proprioception, but acknowledged that this may be due to the imprecision of their test.

It has been suggested that caution should be used in assessing proprioception in the lower limb when assessments are made while subjects are in the seated position [7], as is the case in the above studies. This is because thresholds in the ankle and knee are much lower when measured in the standing, weight bearing position where engagement of the leg muscles is greatly increased [1,3].

In a recent study, Bullock-Saxton et al. [7] assessed the effects of age on the accuracy of a knee joint repositioning test in both full and partial weight-bearing conditions in 60 healthy, pain-free subjects from three age groups (young: 20–35 years old, middle-aged: 40–55 years and older: 60–75 years). They found that subjects in all three groups performed better when full weight bearing than when partial weight bearing, and significant age related increases were found only in the partial weight bearing condition. However, other studies assessing position sense of the ankle joint when weight bearing have reported increased thresholds with age. Thelen et al. [3] compared the ability of young and older women to detect dorsiflexion and plantarflexion movements of the foot when weight bearing on a moveable platform and reported that the threshold for movement detection was 3–4 times larger in the older group. High detection thresholds for inversion and eversion movements of the ankle when standing either unipedally or bipedally on a rotating platform have also been found in older people [8]. Finally, Blaszczyk et al. [3] have reported that old subjects are significantly worse than young subjects in reproducing ankle joint positions when standing on a rotating platform.

Pathology

Reduced proprioception is associated with instability and falls in older people. Hurley et al. found that reduced proprioceptive acuity at the knee was significantly associated with an increased aggregate time to perform a range of function tasks comprising a timed walk, the get up and go test and stair ascent and descent in a combined group of young, middle aged and older people. In large prospective studies Lord et al., impaired lower limb proprioception was also associated with multiple falls in older people living independently in the community [9] and in those living in residential care [10]. Brocklehurst et al. [6] also reported a significant association between impaired proprioception in the ankle and/or great toe and falls in people aged 75–84 years.

Conclusion

There is a significant decline and an increase in variability in proprioception with age, particularly in the lower limbs. Proprioceptive thresholds for the ankle and knee are much lower when measured in the standing, weight bearing position. One study has reported no significant age related change in knee proprioception in this condition, but other studies have reported age related declines in the ankle joint when weight bearing. Reduced peripheral sensation is associated with falls in older people, when the measures of peripheral sensation are accurately and quantitatively ascertained.

References

- Howard IP, Templeton WB (1966) Human spatial orientation. Wiley, London
- Laidlaw RW, Hamilton NA (1937) A study of thresholds in apperception of passive movement among normal control subjects. *Bull Neurol Inst* 6:268–273
- Lord SR, Sherrington C, Menz H (2001) Falls in older people: risk factors and strategies for prevention. Cambridge University Press, Cambridge
- Lord SR, Ward JA (1994) Age-associated changes in sensori-motor changes and balance in community dwelling women. *Age Ageing* 23:452–460
- MacLennan WJ, Timothy JI, Hall MPH (1980) Vibration sense, proprioception and ankle reflexes in old age. *J Clin Exp Gerontol* 2:159–171
- Brocklehurst JC, Robertson D, James-Groom P (1982) Clinical correlates of sway in old age – sensory modalities. *Age Ageing* 11:1–10
- Bullock-Saxon JE, Wong WJ, Hogan N (2001) The influence of age on weight-bearing joint reposition sense of the knee. *Exp Brain Res* 136:400–406
- Gilsing MG, Vanden Bosch CG, Lee SG et al. (1995) Association of age with the threshold for detecting ankle inversion and eversion in upright stance. *Age Ageing* 24:58–66
- Lord SR, Ward JA, Williams P, Anstey K (1994) Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc* 42:1110–1117
- Lord SR, Clark RD, Webster IW (1991) Physiological factors associated with falls in an elderly population. *J Am Geriatr Soc* 39:1194–1200

Proprioception: Effect of Gravity

JAMES R. LACKNER, PAUL DiZIO
Ashton Graybiel Spatial Orientation Laboratory,
Brandeis University, Waltham, MA, USA

Synonyms

Kinesthesia

Definition

Proprioception is the sensory registration of the ongoing spatial configuration of the body. Sherrington invented the term to denote responsiveness to the internal, self-generated state of the body based on mechanoreceptors embedded within body tissues, subserving both conscious awareness and automatic control of posture and movement [1]. The term “kinesthesia” refers more specifically to the awareness of the position and movement of body parts. The perception of force, effort or heaviness relies on some of the same sensory and central mechanisms as proprioception and kinesthesia.

On earth, posture and locomotion are always carried out against the omnipresent force of gravity that accelerates objects downwards toward the earth’s surface. The musculature of the body has to exert forces across the joints to keep the body straight so that it does not buckle and fall to the ground. In this context, proprioception is highly dependent on interrelating signals from the muscle spindle receptors within intrafusal muscle fibers to patterns of alpha and gamma motoneuron activation innervating the muscles that support the whole body or an individual limb against the acceleration of gravity [2]. Golgi tendon organs and Ruffini endings of the joints may participate as well, though their contribution is less well understood. Slowly adapting cutaneous stretch receptors are stimulated by distension of skin overlying moving joints and contribute to the sense of position and movement. The fingertip is especially rich in cutaneous mechanoreceptors and dragging or holding the finger lightly over a stable surface augments the perception and control of arm movements and of locomotor activity. During standing posture, the support surface exerts a contact

force on the soles of the feet that counteracts the downward acceleration of the body's center of mass, and the distribution of the contact forces on the soles of the feet provides information about the orientation of the body to gravity. The vestibular system is an extension of the proprioceptive system because it senses head movement relative to gravity, and various sensor types in the viscera and vasculature [3] also contribute to estimates of body orientation. Although vision and audition are not typically considered part of the proprioceptive system, there are strong interactions among seen, heard and felt body configurations and the localization of external objects [4]. A rough estimation of body configuration and motion could perhaps even be acquired through the sense of smell. These examples illustrate the domain and sources of proprioception.

Characteristics

Higher Level Processes

Dynamic Sensory-Motor Calibrations to 1g

Until relatively recently in history, humans were not exposed to force levels other than the 1g ($g=9.8 \text{ m/s}^2$) background acceleration of Earth gravity, except momentarily, for example during jumping or running or horse riding. With the advent of powered vehicles including aircraft and space craft and orbiting space stations, exposure to weightlessness and to high force fields has become commonplace. On Earth, if an arm is raised, it is subjected to a gravity torque that must be opposed. This torque is not constant but depends on arm angle, see Fig. 1.

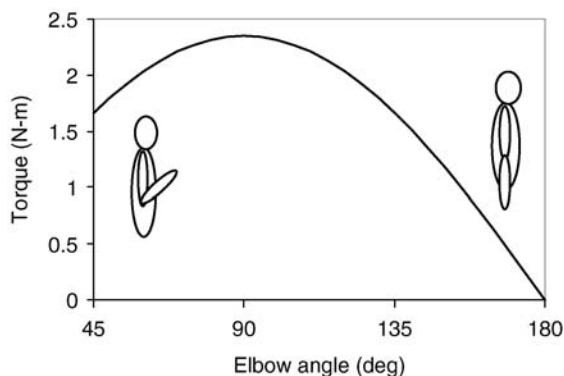
Nevertheless, it seems to require roughly constant effort – except in cases of fatigue – to position the arm relative to gravity. Under normal conditions, one does not sense the different force demands associated with changes in body configuration or body movements relative to gravity. The effects of gravity on movement control seem relatively transparent – as if they were not there. This transparency actually represents a form of

sensory-motor calibration to earth gravity – based on an internal model of the consequences of gravity on body actions, so that equal extents of movement seem equivalent regardless of the actual muscle force demands to achieve them [5].

Muscle spindle gain is affected by background force level. As a consequence, tonic vibration reflexes are attenuated in weightless conditions and augmented in greater than 1g background force levels. These reflexes occur because mechanical vibration of a muscle can excite muscle spindle primary and secondary endings, which leads to a reflexive contraction of the vibrated muscle. The g-dependent modulation of the tonic vibration reflex probably reflects a vestibulo-spinal modulation of the gain of spindle receptors of postural muscles, but could include altered patterns of alpha-gamma coactivation as the load demands on the muscles vary with force level. Studies of arm movement control in non-earth gravity force levels indicate patterns of change consistent with variations in spindle discharge levels [6]. When individuals practice in normal conditions to make arm movements of particular velocities and amplitudes and then attempt the same arm movements in parabolic flight in 0g and 1.8g force backgrounds, they exhibit systematic changes. Movements made at a natural speed in 0g are smaller in amplitude and have more dynamic overshoots of final end positions than movements of the same attempted velocity and amplitude in 1.8g. This pattern is consistent with decreased spindle gain in 0g. With long-term exposure to weightlessness, astronauts display an adaptive modification of their internal model of the effects of gravity on movement, which also may involve a recalibration of proprioception.

Self/Environment Discrimination

Proprioception figures prominently not just in the awareness of ongoing body configuration but also in the maintenance of a stable perceptual distinction between changes in afferent input due to self-motion versus motion of or within the environment. This is reflected in the adaptive resetting of internal models of the environment. The function of these tuning mechanisms becomes apparent when the body is exposed to a background force level different in magnitude from earth gravity. Then, until adaptation occurs, misperceptions of body motion and of the stability of the support surface result. Changes in background force level can be achieved in an aircraft flown in a parabolic trajectory to generate alternating periods of 1.8g (nearly twice Earth gravity) and of weightlessness (0g). In this circumstance, the body alternately becomes much heavier and much lighter than usual respectively. The consequences of this sudden weight change become apparent when an individual attempts to make deep knee bends in the 1.8g background force level [7]. Lowering the body involves eccentric



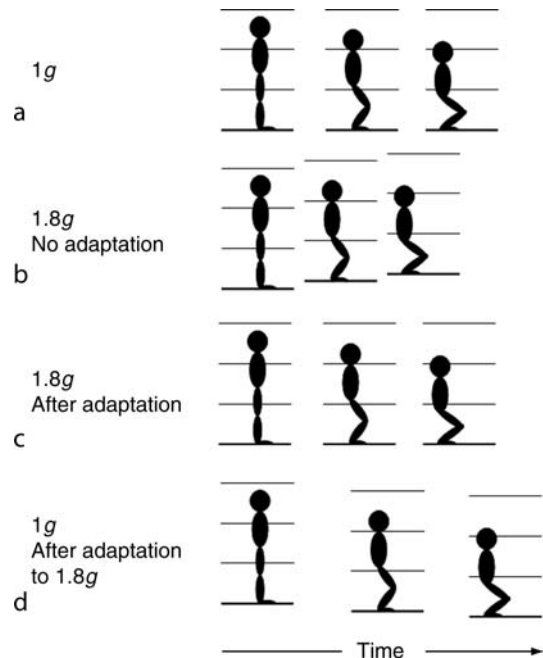
Proprioception: Effect of Gravity. Figure 1 Joint torque.

contraction (controlled lengthening) of the body's antigravity muscles (e.g. the quadriceps and gastrocnemius muscles of the legs). More activation of these muscles will be required during the course of the movement than is the case on earth, otherwise the body would descend too rapidly because of its increased weight. In this situation, the individual will experience him or herself as moving downward too rapidly and the support surface, the deck of the aircraft, as simultaneously rising upward against the feet. To return to the upright, much greater muscular force than normal is required, the body seems to rise too slowly and the aircraft deck seems to move downward. In 0.5g background force levels, the opposite pattern is experienced during deep knee bends. Body weight is less than normal and less muscle force is required throughout the movements. As the body is lowered, it seems to move downward too slowly and the deck simultaneously seems to move downward under the feet. On rising back to the upright, the body feels as if it has moved too rapidly and too far and that the deck floor has simultaneously moved upward under the feet, causing the whole body to displace farther than intended.

If an individual makes repeated deep knee bends during exposure to a steady state non-1g background force level, the movements soon begin to feel more normal and natural and the illusory displacement of the stance surface is correspondingly attenuated. After 50–100 repetitions, the movements will again feel normal and the support surface stable [8]. But then on re-exposure to a normal 1g-force background, deep knee bends will again feel abnormal and the support surface will seem to displace. Fig. 2 shows the patterns of motion and effort experienced on (a) initial exposure to 1.8g force levels in parabolic flight, (b) after the execution of many deep knee bends and (c) on return to normal 1g levels. As illustrated, full adaptation is achieved and the aftereffect experienced is opposite in sign to the effects experienced during initial exposure to the abnormally high force level.

This pattern means that motor control and position sense are recalibrated during exposure to the 1.8g force level and that this recalibration carries over on return to 1g where it is inappropriate. Animals evolved in the context of a 1g-background force level without any experience with steady state non-1g force levels. Nevertheless, significant adaptation to an unusual background force occurs within seconds or a few minutes.

The factors underlying adaptation to an increased force background can be understood as follows. As the body lowers in a deep knee bend in a 1.8g force background, the antigravity muscles that undergo controlled lengthening will be longer than normally would be the case for the levels of alpha and gamma motoneuron activation present, because body weight has nearly doubled. Consequently, these muscles need to be innervated at higher than normal levels. Signals from the spindle receptors within the muscles will be



Proprioception: Effect of Gravity. Figure 2

(a) Schematic illustration of the sequence of actual and perceived events as one descends in a deep knee bend. (b) During the first deep knee bend made in 1.8g, one's body seems to descend too fast while the floor (*thick lines*) and visual surround (*thin lines*) rise. (c) After adaptation to 1.8g, self motion is perceived normally and the environment feels stable. (d) Returning to 1.0g elicits after effects opposite to the original illusion in 1.8g, until re-adaptation is complete.

higher than normal also, because the spindles are under a greater degree of loading than normal. Position sense is generated in part by the CNS comparing patterns of spindle feedback with patterns of alpha-gamma activity. If the pattern of spindle feedback is aberrant in relation to the alpha-gamma activation patterns, a distortion of position sense occurs. Abnormally high levels of spindle activity in skeletal muscles evoke misperceptions of the joint positions controlled by the muscles, with the muscles being interpreted as being longer than they actually are. For example, an abnormally high level of quadriceps activity is associated with the knee joint being perceived as more flexed than it actually is.

When deep knee bends are initially made during exposure to 1.8g, the abnormally high spindle activity levels present in relation to the alpha motoneuron activity are interpreted as the legs being more flexed during the course of the lowering movement than they actually are. The CNS attributes this to external motion, the aircraft deck rising under the feet causing the knees to be more flexed than intended. With repetition the deep knee bends feel progressively more normal as the

relationship between body movement, motor commands and expected spindle feedback is remapped in the internal model of movement control to be the “normal” state of affairs. On return to normal 1g background force levels, the relationship between motor commands and spindle feedback will again be abnormal. As the body is lowered, less innervation of the antigravity muscles will be necessary than in 1.8g to control the lowering of the body. Consequently, the spindle feedback generated will be less than expected; this is interpreted as the legs being less flexed than intended and attributed to the deck moving downward under the feet, preventing the knees from bending appropriately.

Proprioception and the Body Map

That individuals born without a limb can still experience a phantom limb (see Phantom limb sensations and pain) attests to the fact that a map of body segments and their connectedness exists in the brain, which is complementary to proprioception. We normally experience this map as a sense of body topology, the connectedness of a set of body segments. This map both governs proprioception and can be altered transiently or be semi-permanently remapped by proprioceptive inputs, as shown by vibratory myesthetic illusions. For example, illusory forearm extension is perceived if 120 Hz vibration is applied over the biceps of the restrained arm. The perceived finger trajectory is constrained by the internal map, which represents the forearm with a specific length and the biceps muscle as acting across the elbow joint. However, if the index finger of the vibrated arm is touching the nose then illusory elongation of the nose is perceived simultaneously with arm extension, violating the internal mapping of the nose as a non-jointed semi-rigid body part [9]. Longer-term vibrotactile skin stimulation alters the cortical somatosensory map.

Multisensory Body Maps

Multiple, interdependent representations of hand and arm position exist which are influenced by visual and muscle spindle inputs. This interdependence has been demonstrated in experiments involving vibratory myesthetic illusions of the forearm in a dark room with the test subject’s finger made visible by phosphorescent paint [4]. When subjects feel their forearm move, they also see their finger move as well but through a smaller distance. The magnitude of felt motion of the forearm is greater in darkness than with the finger visible. Thus, vision affects the proprioceptive representation because the optically stationary finger attenuates felt motion, and proprioception affects the visual representation because the vibration-induced muscle spindle afferent signal makes the optically stationary finger appear to move.

If a visual-proprioceptive discrepancy is introduced for a longer exposure period, then semi-permanent

adaptive changes in proprioception can occur. The nature of these changes depends on the exposure conditions. For example, a seated subject wearing laterally displacing prism spectacles will initially miss when pointing to a visual target. However, if the subject continues to reach and is allowed visual feedback of the reaches, accuracy will soon be regained. The adaptive change involves an arm-torso recalibration in terms of an internal shift in the felt position of the exposed arm but not of the other arm [10]. The adapted subject still wearing the prisms will reach accurately to the real target but see and feel the arm in its optically displaced location. The felt arm position then does not correspond to the real arm position but it does correspond to the visual arm position. By contrast, if subjects are allowed to walk around wearing the prism spectacles they are clumsy at first but ultimately learn to navigate. They also gradually adopt a deviated head posture but feel their head to be straight on their torso. This internal proprioceptive remapping of head to torso allows accurate body-relative localization and normal control of locomotion.

Pathology

With the advent of manned space flight, humans have been exposed to weightless conditions for prolonged periods. On return to earth, they exhibit a variety of derangements of posture and gait. These disturbances are related to adaptive changes in neuromuscular structure and control occurring in weightless conditions that are inappropriate for terrestrial conditions. Post-flight, when astronauts walk, the ground feels unstable under their feet and their movements require greater than normal effort. The simplest movement, e.g. raising the arm, can feel as if it requires immense effort and force. If the astronaut does a deep knee bend, then it feels as if he or she has moved downward too rapidly and that the ground has simultaneously moved upward. Precisely the same patterns are experienced as those by individuals, as described above, who are adapted to earth gravity and make deep knee bends in the high force phases of parabolic flight. These changes reflect the decreased muscle spindle gain associated with weightless conditions and the lack of appropriate contact cues to signal body orientation and configuration.

Proprioceptive loss is characteristic of a variety of diseases and injuries of the nervous system. The most severe cases involve loss in adulthood of large somatic sensory fibers, including muscle spindle, joint, tendon and cutaneous mechanoreceptor afferents. An affected individual with eyes closed has no ability to localize his or her limbs even during vigorous active or passive movement. Standing and walking in darkness are not possible. Affected individuals can reacquire functional movement using visual guidance. Even partial loss of proprioception has severe consequences for balance and locomotion.

In summary, the human body has a dynamic sensory-motor spatial calibration to Earth gravity. This calibration involves an internal model of the force background and its consequences for voluntary movement control. The calibration is continuously updated based on experience within the environment. Somatosensory, proprioceptive and visual signals contingent on self-produced movements are key elements contributing to updating. The continuous ongoing nature of the calibration process is probably why movement control adjusts so rapidly when the body is exposed to force backgrounds greater or less than 1g in magnitude and why patients can adapt to proprioceptive loss.

References

1. Sherrington CS (1948) The integrative action of the nervous system. Cambridge University Press, London
2. Matthews PBC (1988) Proprioceptors and their contribution to somatosensory mapping: complex messages require complex processing. *Can J Physiol Pharmacol* 66:403–438
3. Magnus R (1924) Körperstellung. Springer, Berlin Heidelberg New York
4. Lackner JR, Taublieb A (1984) Influence of vision on vibration-induced illusions of limb movement. *Exp Neurol* 85:97–106
5. Lackner JR, DiZio P (2000) Aspects of body self-calibration. *Trends Cogn Sci* 4:279–288
6. Fisk J, Lackner JR, DiZio P (1993) Gravitoinertial force level influences arm movement control. *J Neurophysiol* 69:504–511
7. Lackner JR, Graybiel A (1981) Illusions of postural, visual, and substrate motion elicited by deep knee bends in the increased gravitoinertial force phase of parabolic flight. *Exp Brain Res* 44:312–316
8. Lackner JR, DiZio P (1993) Spatial stability, voluntary action and causal attribution during self-locomotion. *J Vestib Res* 3:15–23
9. Lackner JR (1988) Some proprioceptive influences on the perceptual representation of body shape and orientation. *Brain* 111:281–297
10. Harris CS (1963) Adaptation to displaced vision: visual, motor, or proprioceptive change? *Science* 140:812–813

Proprioception: Effect of Neurological Disease

JONATHAN COLE
COPMRE, University of Bournemouth and Poole
Hospital, Dorset, UK

Synonyms

Large-fiber sensory neuronopathy and neuropathy; Sensory ataxia; Dorsal column ataxia; Sensory stroke

Definition

Loss of movement and position sense due to disease of the peripheral or central nervous system.

Characteristics

The perceptions of movement and position sense, as well as that of touch, are dependent on afferent information relayed by large myelinated sensory nerve fibers, with cell bodies in the dorsal root ganglia and which then ascend in the ipsilateral dorsal columns (DCs). They synapse in the dorsal column nuclei at the head of the spinal cord. The pathway then projects through the medulla in the medial lemniscus to synapse in the ventral-posterior thalamus and hence, via the internal capsule, to the sensory cortex. Within the brain information is relayed to coordinate movement as well as give consciousness of the position and movement states of the body and limbs. Loss of ►proprioceptive information can lead to in-coordination due to dysfunction in the motor cortex and the cerebellum. In-coordination due to peripheral ►deafferentation and cerebellar lesions can sometimes be difficult to distinguish completely.

Disease anywhere along the above pathways can result in ►proprioceptive loss, usually with cutaneous sensory loss. While selective losses are possible, in particular in the peripheral nerve cell and to an extent in the dorsal columns, more central lesions may also affect other areas, making the resultant physiological deficit more complex. Often, for instance, cortical lesions lead to reduced stereognosis (inability to manipulate and recognize objects placed in the hand without vision) and graphesthesia (ability to recognize figures touched over the hand without vision), as well as in reductions in cutaneous touch and ►proprioception.

►Proprioception is such a deep sense that in folk psychology terms it is almost unknown. People may imagine being blind or deaf, but not being without proprioception or touch. Diderot considered that of all the senses touch (and one presumes the then undiscovered ►proprioception) the most profound and philosophical. To understand what ►proprioception does therefore it is important to consider those rare individuals who have to live without it—without their witness the experience, and its effects on movement, are almost impossible to know.

Total loss of ►proprioception is rare but has been described in the ►acute sensory neuronopathy syndrome. Its effects initially are a complete inability to control or coordinate movement. When movements are made they are inappropriate in size and direction with poor coordination between both limbs and joints. With time, however, and with considerable conscious attention towards, and visual observation of, movement, people without movement or position sense may be able to move in such a fashion as to be almost able to pass unnoticed, in uncluttered, well lit areas (see Section on ►Large-Fiber Sensory Neuropathy).

Though these complete losses of ►proprioception are rare their importance is that they reveal both the consequences of the loss and the ability of subjects, at least partially, to mitigate its effects. In addition, there are less severe yet still important losses of ►proprioception associated with various neurological problems, from median nerve compression at the wrist to central strokes in which motor weakness predominates which may have clinical consequences and yet are often poorly recognized.

Pathology

Peripheral Neuropathy/Neuronopathy

The most pure form of ►proprioceptive loss is disease of the large myelinated sensory nerve fibres, either in their axons or their cell bodies (see Section on ►Large-Fiber Sensory Neuropathy). Lesser, but still important, losses of ►proprioception can occur with less selective sensory peripheral neuropathy, especially affecting the legs, leading to ataxia and a feeling of not knowing where the feet are unless they are looked at. Patients may volunteer that they are much worse in the dark and that they find it difficult to drive a car (because of the need to control foot pedals).

The division between cutaneous light touch and ►proprioception can also be somewhat artificial. In the hands and the face cutaneous information about stretch and deformation of the skin gives information about position. Then, loss of cutaneous sensation has effects on movement. This is sometimes seen in carpal tunnel syndrome. Patients with sensory loss in the thumb and first and second fingers may say they drop things, unless they look at them and think about it, without knowing why. Even small losses of cutaneous touch in the fingers may have effects on the coordination of grip strength and active touch.

Dorsal Column Disease

►Proprioceptive (and cutaneous) afferents ascend with the spinal cord in the dorsal columns; disease of these structures is a well-known cause of loss of movement and position sense. One well-known cause of ►ataxia due to DC loss is vitamin B₁₂ deficiency.

Sub-acute combined degeneration of the spinal cord involves the dorsal and lateral columns of the spinal cord and presents often, in middle age, with ►parasthesiae of the feet, with tingling and even burning [1]. Difficulties in walking follow, if untreated, due to sensory ►ataxia and motor weakness, reflecting lateral (motor) column involvement. Loss of postural sense can be more severe than the cutaneous sensory deficit. These may be accompanied by optic atrophy and cognitive impairment. The pathology involves both demyelination and axonal loss and treatment is usually effective, especially if given early [2].

Historically, syphilis was a major pathogen affecting the dorsal columns (Wilson, 1940 for a clinical

description of neurosyphilis) [3]. Tabes dorsalis usually emerges 10–25 years after the initial infection and can present with progressive ►ataxia and a high stepping gait, and with severe, intermittent, “lightning” pains in the legs and abdomen. More rarely, it can also be seen far earlier in congenital syphilis. The pathology may be demyelination and destruction of the dorsal roots. In this form of syphilis it is not solely the DCs that are affected; failing vision, impotence, deafness and arthropathy and ulceration, reflecting small fiber loss too, are often associated with it.

Others causes of DC loss are multiple sclerosis with a plaque involving the dorsal cord, tumor and, most rarely, penetrating wounds in the neck with DC dissection. It has also been associated with a rare form of retinitis pigmentosa, which offers the possibility to understand the genetic nature of DC delineation [4].

Intracerebral Lesions

Pure sensory ►ataxias after sub-cortical stroke, or plaque or tumor are rare, since these diseases do not affect single pathways or classes of neuron. For instance, Russmann et al. [5] analyzed the Lausanne Stroke Registry between 1986 and 1998 for those with an ischemic episode affecting the area of the lenticular nucleus. Of 820 consecutive patients, 13 had pure lenticular infarction with four having an ataxic sensorimotor hemisindrome, presumably due to a lesion of the internal capsule. Though examples of pure sensory stroke after small lacunar infarcts have been described after infarcts in the ventral posterior thalamus, brain stem, internal capsule and cerebral cortex, more often central lesions lead to more complex and subtle deficits.

It can, for instance, be difficult to distinguish, at the two extremes, between a pure motor weakness from an ►ataxia from in-coordination due to sensory loss. Kim [6] analyzed a group of patients with thalamic stroke with motor and sensory problems. ►Ataxia and involuntary movements were seen most after sensory loss, with ►dystonia, and in-coordination of movements associated with proprioceptive loss. Central sensory loss due to stroke can also be associated with dysesthesia and pain.

Though the commonest pathology associated with pure sensory stroke is ischemia, this syndrome occurs after hemorrhagic stroke too [7]. Pontine strokes involving the medial lemniscus, but sparing the spinothalamic tracts, lead to selective loss of vibration sensitivity and proprioception without an effect on pinprick and temperature sensation. More rostral strokes do not always lead to pure loss of proprioception as the dorsal column/medial lemniscal and the spinothalamic tracts become closer within the brain. Thus some thalamic strokes may lead to loss of all modalities of sensation over the opposite side of the body, with reduced temperature sensation and pin prick sensation as well as dysesthesia.

In central pure stroke syndromes Fisher [8] suggested that though objective sensory disturbances can be mild, larger losses are seen in fine motor control and coordination of the hand and fingers. This may reflect on the one hand the relative insensitivity of clinical tests of sensation, and the possible use of other cortical areas for these discriminations, and on the other the crucial importance of parietal cortex in the coordination of finger movements. Occasionally this role of the cortex in movement leads to confusion as to whether weakness is peripheral, say due to an ulnar nerve lesion, or cortical [9]. A relative lack of sensory symptoms and preserved power with clumsiness and reduced coordination may point towards a cortical deficit.

In addition it is important to realize that mixed sensory-motor strokes can prove difficult to rehabilitate due to underlying **proprioceptive** loss over and above the more obvious problems with motor weakness. Loss of information about movement and position superimposed on loss of power can add a significant additional problem, especially if not recognized. Correspondingly, there are some reports that exercises designed to improve coordination can add to any spontaneous recovery that occurs [10].

Though syndromes involving exclusively loss of movement and position sense are very rare in neurology, an awareness of the effects of proprioceptive loss may allow greater understanding of mixed sensory and motor syndromes and lead to different rehabilitation strategies.

References

1. Hemmer B, Glocker FX, Schumacher M, Deuschl G, Lucking CH (1998) Subacute combined degeneration: clinical, electrophysiological, and magnetic resonance imaging findings. *J Neurol Neurosurg Psychiatry* 65:822–827
2. Thomas PK (1998) Subacute combined degeneration. *J Neurol Neurosurg Psychiatry* 65(6):607
3. Wilson SAK (1940) Neurosyphilis. In: Bruce AN (ed) *Neurology*, vol 1. Edward Arnold, London, pp 455–469
4. Higgins JJ, Morton DH, Loveless JM (1999) Posterior column ataxia with retinitis pigmentosa (AXPC1) maps to chromosome 1q31–q32. *Neurology* 1:46–50, 52
5. Russmann H, Vingerhoets F, Ghika J, Maeder P, Bogousslavsky J (2003) Acute infarction limited to the lenticular nucleus: clinical, etiologic, and topographic features. *Arch Neurol* 60:351–355
6. Kim JS (2001) Delayed onset mixed involuntary movements after thalamic stroke: clinical, radiological and pathophysiological findings. *Brain* 124:299–309
7. Shintani S, Tsuruoka S, Siigai T (2000) Pure sensory stroke caused by a cerebral hemorrhage: clinical-radiologic correlations in seven patients. *Am J Neuroradiol* 21:515–520
8. Fisher CM (1965) Lacunes: small deep cortical infarcts. *Neurology* 15:774–784
9. Timsit S, Logak M, Manai R, Rancurel G (1997) Evolving isolated hand palsy: a parietal lobe syndrome associated with carotid artery disease. *Brain* 120:2251–2257
10. Smania N, Montagnana B, Faccioli S, Fiaschi A, Aglioti SM (2003) Rehabilitation of somatic sensation and related deficit of motor control in patients with pure sensory stroke. *Arch Phys Med Rehabil* 84:1692–1702

Proprioception: Role of Cutaneous Receptors

DAVID F. COLLINS

Faculty of Physical Education and Recreation,
Centre for Neuroscience, University of Alberta,
Edmonton, AB, Canada

Definition

Proprioception and Kinesthesia

The term proprioception (proprius = Latin for “one’s own”) describes abilities related to the perception of different aspects of one’s own movement. These include the sense of the position and movement of the body segments (kinesthesia) as well as sensations related to tension in muscles and tendons, balance and voluntary effort [1]. This essay reviews the evidence that cutaneous receptors contribute to kinesthesia, the ability to detect the position and movement of the body segments without using vision. Cutaneous receptors are sensory receptors located in the skin. During movement, the skin is stretched and compressed, activating cutaneous receptors in large areas of skin around the moving joint (Fig. 1) [2].

The pattern of skin strain is different for movements of different speeds and amplitudes and this information is encoded in signals from large numbers of receptors that discharge during movement. These signals travel along peripheral nerves to the spinal cord and pass to the brain where, along with feedback from sensory receptors in muscles and joints, they provide the information responsible for kinesthetic awareness and proprioceptive judgments (see **Proprioception: Role of Muscle Receptors and Proprioception: Role of Joint Receptors**). Kinesthetic information is used for the planning and execution of movement.

Characteristics

Sensory Receptors and Kinesthesia

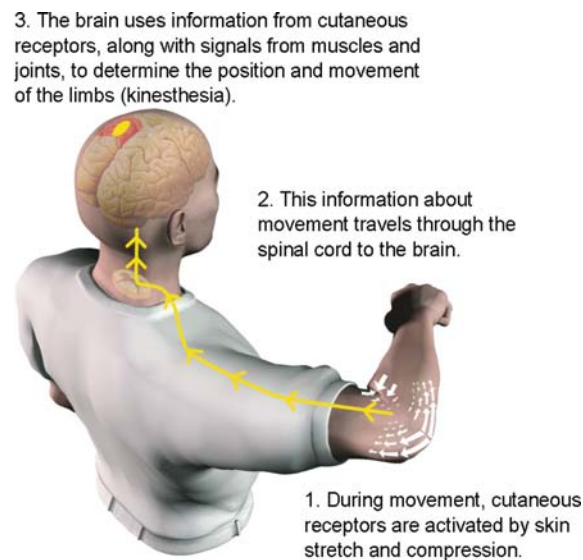
During movement, sensory receptors in muscles, joints and the skin send movement-related information to the brain where it is used for kinesthesia. For more than 30 years, it was thought that the muscle spindle, a

specific type of muscle receptor, was the most important source of kinesthetic information [1,3]. Muscle spindles respond to muscle stretch and thus signal the changes in muscle length that occur during joint movement. Many experiments have shown that this information is important for kinesthesia, such as those investigating the strong illusions of movement that are produced when vibration is applied over a muscle or its tendon. Vibration causes spindles to discharge rapidly and results in powerful illusions of movement consistent with lengthening of the vibrated muscle. Recently, experiments have shown that movement illusions can

also be generated by activating cutaneous receptors by stretching the skin around a stationary joint to mimic skin stretch patterns that occur during normal movement [4,5]. An example of one experiment is shown in Fig. 2 where skin stretch applied around the right elbow resulted in the illusion of elbow flexion (left panel).

The subject matched these illusory movements of the right elbow with voluntary movements of the left arm. These movement illusions initiated by skin stretch show that cutaneous receptors are also important for kinesthesia. Movement illusions also occur when skin stretch is applied around the fingers [4,5] (see Fig. 3) and knee [5]; thus cutaneous feedback is important for kinesthesia at joints throughout the body [5].

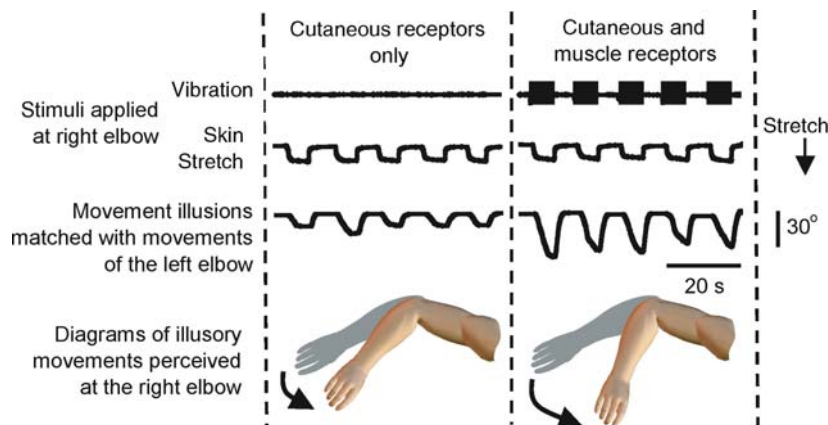
When skin stretch and vibration are applied simultaneously, movement illusions are larger than when either stimulus is applied alone (see Figs. 2 and 3). Hence, the brain uses a combination of information from muscle spindles and cutaneous receptors for kinesthesia. The role played by joint receptors for kinesthesia is unclear, but the decrease in the ability to detect movement when joint receptor feedback was removed by anesthesia suggests they also contribute [3].



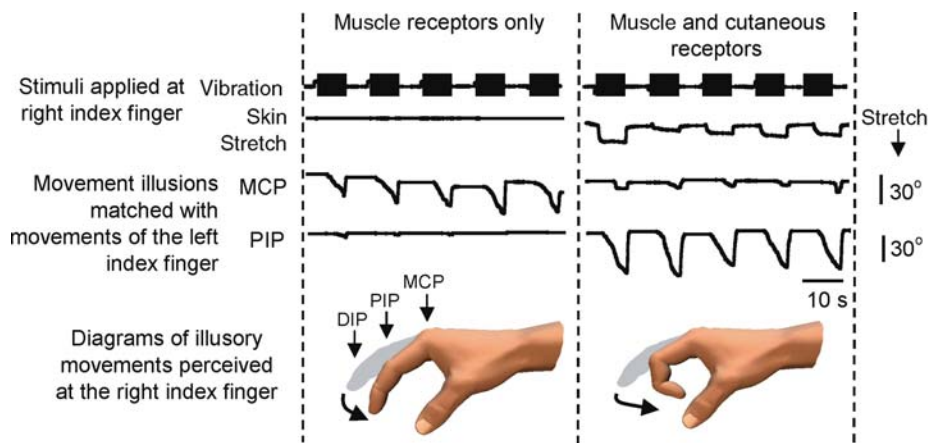
Proprioception: Role of Cutaneous Receptors.
Figure 1 Schematic representation of the role of cutaneous receptors for kinesthesia at the elbow.

Cortical Structures and Kinesthesia

Kinesthetic information from sensory receptors enters the spinal cord through the dorsal horn and ascends to the brain along the dorsal columns. Before entering the brain the pathway crosses over to the opposite side of the body and projects to the main receiving area for kinesthetic information, the primary somatosensory cortex (shown in red in Fig. 1). Here, information from different parts of the body is received in different regions, resulting in a representative map of the body called a homunculus (Latin for “little man”). In the homunculus, regions of the body with the greatest



Proprioception: Role of Cutaneous Receptors. Figure 2 Movement illusions of the elbow produced by stimulating cutaneous receptors alone (skin stretch) or with simultaneous stimulation of receptors in muscle (vibration). Stimuli were applied to the right elbow and subjects matched perceived movements with voluntary movements of the left elbow. Adapted from Collins et al. 2005 [5].



Proprioception: Role of Cutaneous Receptors. **Figure 3** Movement illusions produced at the index finger by stimulating muscle receptors alone (vibration) or with simultaneous stimulation of cutaneous receptors (skin stretch). The skin stretch was applied around the two distal joints (PIP, DIP) and the vibration was applied over a tendon on the back of the hand near the MCP joint. Subjects matched perceived movements with voluntary movements of the left index finger. Adapted from Collins et al. 2005 [5]. (MCP metacarpophalangeal joint; PIP proximal interphalangeal joint; DIP distal interphalangeal joint)

numbers of receptors, such as the hands, have the largest representation. The perception of movement, however, is not localized to this one part of the brain but involves activity in many brain regions [6]. Thus, kinesthesia is a distributed process involving the somatosensory cortex as well as the motor cortex, cerebellum and frontal parts of the cortex with a particular importance of the right hemisphere [6].

Lower Level Components

Cutaneous Receptors

Much of our knowledge about cutaneous receptors comes from work on the hand where four morphologically distinct types of receptor have been identified [7]. Merkel discs and Meissner corpuscles lie in the superficial layers of the skin and have relatively small receptive fields ($\leq 10 \text{ mm}^2$). Densities for these receptors are highest in the distal skin, with the digit tips containing 70 and 140 receptors/ cm^2 for Merkel discs and Meissner corpuscles, respectively [7]. Pacinian corpuscles and Ruffini endings reside in the deeper layers and have larger receptive fields ($\leq 25 \text{ mm}^2$) and densities that are lower and more uniform [7]. Meissner and Pacinian corpuscles adapt rapidly to sustained stimuli such as constant velocity movements and discharge primarily at the beginning and end of movement. In contrast, Merkel discs and Ruffini endings adapt slowly to sustained stimuli and continue to discharge throughout movement with a discharge frequency that is often closely related to the amplitude and velocity of the movement. Receptors similar to those in the hand have also been found in the skin of the arm and leg, although there are regional differences in receptor densities.

Higher Level Processes

Sensory Feedback and Movement Control

The control of human movement involves a complex interaction between motor output from the brain and sensory feedback from peripheral sensory receptors. Sensory feedback from the limbs provides information about movement execution, sending an error signal to the brain when movements do not proceed as planned. Sensory feedback also contributes to movement control at the level of the spinal cord. Spinal reflexes provide automatic responses to external disturbances that help to prevent for example slips of hand-held objects [7] or trips during walking. Sensory feedback also influences the timing and amplitude of muscle contractions during rhythmic movements by modifying the activity of central pattern generators in the spinal cord that are responsible for generating the basic patterns of muscle activity.

Lower Level Processes

Communication in the Nervous System

Information travels through the nervous system in the form of action potentials, tiny electrical impulses generated by the transient passage of ions across the cell membrane. During movement, action potentials are initiated in a cutaneous receptor during movement of the skin within its receptive field. These signals travel along myelinated axons of the nerve cells (neurons) at 35–80 m/s to synaptic junctions with other neurons. At the synapse, the site for communication between neurons, the arrival of the action potential triggers the release of neurotransmitter, a chemical signal that activates receptors on the membrane of the post-synaptic neuron. Receptor activation initiates

ion movement across the post-synaptic membrane where, with a sufficiently large stimulus, another action potential is generated. Thus, communication between neurons (synaptic transmission) involves the conversion of an electrical signal (action potential) into a chemical signal at the synapse and back to an electrical signal in the post-synaptic cell.

Process Regulation

Gating of Cutaneous Feedback During Movement

Transmission along pathways from cutaneous receptors to the brain is suppressed during movement [8]. This suppression occurs in the spinal cord and brain and is thought to prevent these structures from becoming saturated by the massive amount of sensory traffic that is generated during movement. Control of information flow through the nervous system is selective; irrelevant signals are suppressed more than signals from receptors that provide information that is important for the successful performance of the movement [8].

Function

The Cutaneous Contribution to Kinesthesia

For many years it had been thought that cutaneous receptors play only a minor role in kinesthesia, perhaps acting to facilitate movement-related feedback from muscle spindles. This “facilitation” hypothesis was tested by measuring the ability to detect small finger movements when cutaneous feedback from adjacent digits was removed (by anesthesia) or enhanced (by skin stimulation) [9]. Movement detection was not decreased by cutaneous anesthesia nor was it enhanced by increasing cutaneous receptor discharge. Thus, the role for cutaneous feedback for kinesthesia is not one of general facilitation [9]. Instead, evidence has been mounting over the last 10 years that cutaneous receptors provide specific information about the movement itself [2] and this is used for kinesthesia [4,5]. Some idea of the relative roles of feedback from cutaneous receptors and muscle spindles has come from experiments investigating illusory movements of the fingers using vibration to activate muscle spindles and skin stretch to activate cutaneous receptors around specific finger joints (Fig. 3) [4,5]. When vibration was applied by itself, subjects perceived movements primarily at the metacarpophalangeal (MCP) joint (Fig. 3, left panel). When the skin around the proximal and distal interphalangeal joints was stretched and compressed during vibration, to mimic patterns that occur during movements of those joints, the perception of movement decreased at the MCP joint and increased at the joints where the skin stretch was applied. This supports the idea that one role for cutaneous feedback may be to help to distinguish which finger joint is moving [5]. Most muscles that control movements of the fingers are located in the forearm and cross more than one joint.

Hence, the changes in muscle length detected by muscle spindles could arise from movement at one or more joints. The proximity of cutaneous receptors around individual joints enables them to provide specific information about which joint is moving. The receptors most likely to provide this information are the rapidly adapting Pacinian and Meissner corpuscles [2]. Information from the slowly adapting receptors, particularly the Ruffini endings, is more likely to be responsible for providing ongoing information about the position and velocity of the moving joint [2]. Cutaneous feedback is also important for kinesthesia at the elbow and knee and it is likely that feedback from muscle spindles and cutaneous receptors is used for kinesthesia for joints throughout the body [5].

Pathology

Clinical Implications

The idea that cutaneous receptors contribute significantly to kinesthesia is relatively recent and the clinical implications have yet to be fully explored. It had been suggested that improvements in joint stability associated with bandaging the knee might be due to enhanced cutaneous proprioception, but this was not supported by experiments assessing movement detection with and without a bandaged knee [10]. However, the cutaneous contribution to kinesthesia should be considered for tests of proprioception that make up part of standard neurological examinations. Clinicians should be careful to avoid generating conflicting signals from cutaneous receptors when applying passive joint movements. Finally, one would predict that persons who have suffered burns to large regions of skin would have reduced kinesthetic ability due to decreased cutaneous feedback and this may influence movement performance. An increased understanding of the importance of cutaneous receptors for kinesthesia may lead to new ideas for the treatment and assessment of movement disorders.

References

1. Proske U (2005) What is the role of muscle receptors in proprioception? *Muscle Nerve* 31:780–787
2. Edin BB, Abbs JH (1991) Finger movement responses of cutaneous mechanoreceptors in the dorsal skin of the human hand. *J Neurophysiol* 65:657–670
3. Gandevia SC (1996) Kinesthesia: roles for afferent signals and motor commands. In: Rowell LB, Shepherd JT (eds) *Handbook of physiology*. Oxford University Press, New York, pp 128–172
4. Collins DF, Prochazka A (1996) Movement illusions evoked by ensemble cutaneous input from the dorsum of the human hand. *J Physiol* 496:857–871
5. Collins DF, Refshauge KM, Todd G, Gandevia SC (2005) Cutaneous receptors contribute to kinesthesia at the index finger, elbow, and knee. *J Neurophysiol* 94:1699–1706

6. Naito E, Roland PE, Grefkes C, Choi HJ, Eickhoff S, Geyer S, Zilles K, Ehrsson HH (2005) Dominance of the right hemisphere and role of area 2 in human kinesthesia. *J Neurophysiol* 93:1020–1034
7. Johansson RS (1996) Sensory and memory information in the control of dexterous manipulation. In: Lacquaniti F, Viviani P (eds) *Neural bases of motor behaviour*. Kluwer, Netherlands, pp 205–260
8. Brooke JD (2004) Somatosensory paths proceeding to spinal cord and brain – centripetal and centrifugal control for human movement. *Canadian J Physiol Pharmacol* 82:723–731
9. Refshauge KM, Collins DF, Gandevia SC (2003) The detection of human finger movement is not facilitated by input from receptors in adjacent digits. *J Physiol* 551:371–377
10. Hewitt BA, Refshauge KM, Kilbreath SL (2002) Kinesthesia at the knee: the effect of osteoarthritis and bandage application. *Arthritis Rheum* 47:479–483

Proprioception: Role of Joint Receptors

VAUGHAN G. MACEFIELD

Professor of Integrative Physiology, School of Medicine, University of Western Sydney, Sydney, NSW, Australia

Conjoint Principal Research Fellow, Prince of Wales Medical Research Institute, Sydney, NSW, Australia

Synonyms

Kinesthesia; Joint sense; Position sense; Movement sense

Definition

Proprioception, literally the “sense of self” (from Latin “*proprius*” = “own”), is the group of sensory modalities that allow us to know the positions of our limbs in space and to detect and assess the magnitudes of movements and forces without vision. Classically, it had been assumed that this sense was subserved by joint receptors, specialized mechanoreceptors located in the capsular tissues of a joint. Indeed, the term “joint sense” – the capacity to detect movements or changes in position about a joint – is still used in clinical practice, though it is generally now accepted that joint receptors themselves do not bear primary responsibility for our proprioceptive acuity. Muscle spindles – exquisitely sensitive intramuscular stretch receptors – are generally believed to be the sensory endings primarily responsible. Perceptions of joint movement evoked by small amplitude vibration applied to muscles or tendons, either intact or surgically exposed, were the first convincing demonstrations that these receptors contribute importantly to proprioception

(see ►[Proprioception, Role of Muscle Receptors](#)). The role of stretch receptors in the skin has come to increased prominence of late and there are many convincing studies implicating significant roles for cutaneous afferents in proprioception (see ►[Proprioception, Role of Cutaneous Receptors](#)).

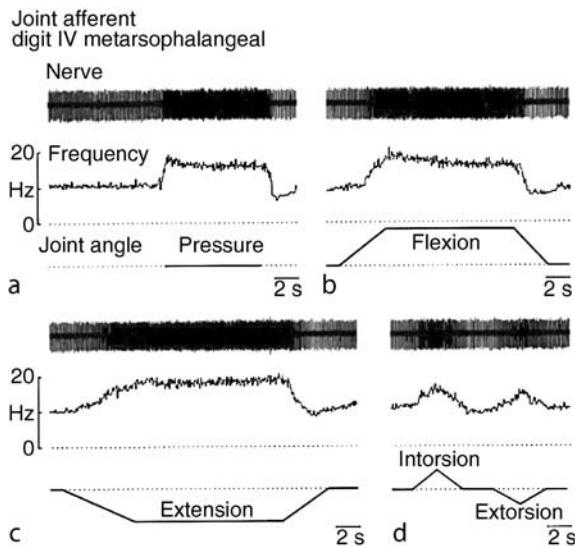
Characteristics

Quantitative Description

The consensus from the animal literature is that joint afferents mostly respond at the extremes of joint rotation [1]. Microelectrode recordings from the median and ulnar nerves of conscious human subjects have shown that mechanoreceptors associated with the interphalangeal joints and metacarpophalangeal joints do not respond to forces applied to bone when there is no movement of the joint and have very high mechanical thresholds to indentation applied over the joint capsule [2,3]. While they do respond to joint movements, they respond primarily at the limits of angular excursion. An example of a recording from a human joint receptor is shown in Fig. 1. This unit, located within the metatarsophalangeal joint of the fourth toe was spontaneously active at rest and responded to imposed extreme plantarflexion and dorsiflexion of the joint and to (unphysiological) internal and external rotation of the joint. Because joint afferents often respond in both directions (e.g. flexion and extension) and in more than one axis of rotation (e.g. abduction/adduction and extorsion/intorsion), as a group, joint afferents have a very limited capacity to encode changes in joint position. Nevertheless, a small proportion of interphalangeal joint afferents do respond across the physiological range [2,3]. Moreover, there is evidence that afferents associated with the dorsal aspects of human metacarpophalangeal joints consistently respond throughout the physiological range of joint rotation [4].

Lower Level Components

Much of the early work on joint receptors, carried out mostly in the knee joint of the cat, supported the idea that joint receptors could encode changes in joint position [5]. However, it turned out that many of these were actually muscle spindle afferents coursing through the nerve supplying the joint. Nevertheless, a few receptors – unequivocally articular in origin – have been found that respond throughout the physiological range of angular excursion [6]. Histological and physiological studies have shown that mechanoreceptors in the posterior capsule of the cat knee joint, identified as Ruffini organs (i.e. similar to the stretch receptive SAI endings in skin) respond in a slowly adapting manner to strains applied in the plane of the tissue but have very high thresholds to compressive stresses applied perpendicularly – the adequate stimulus is the increase in tensile strain in the immediate environment of the receptor [7]. Ruffini endings have also been identified



Proprioception: Role of Joint Receptors.

Figure 1 Microelectrode recording from a joint afferent associated with the metatarsophalangeal joint of the fourth toe in conscious human subject. The mechanoreceptor responded to pressure over its receptive field (a) and to passive flexion (b), extension (c) and longitudinal rotation of the joint (d). Changes in joint angle are represented schematically.

in the human finger and knee joints and the discharge behavior of human joint afferents associated with the interphalangeal and metacarpophalangeal joints fits with their being Ruffini endings; they have very high mechanical thresholds to indentation applied over the joint capsule and respond to joint movements that cause an increase in tensile strain within the joint capsule [2].

Higher Level Processes

Proprioceptive acuity is optimal when inputs from muscle, skin and joints are intact [8]. Anesthesia of the joint capsule attenuates and intra-articular fluid expansion augments proprioceptive acuity at the interphalangeal joint, arguing for a role of joint afferents in proprioception [9]. Intraneural microstimulation of a single joint afferent in conscious human subjects can be perceived as pressure over the joint or as a small movement, so joint afferents do have a strong synaptic coupling to higher order sensory neurons [3]. This means that, should a joint receptor be exposed to an adequate tensile strain within the joint capsule or extracapsular ligament, it could provide useful information. But given that these tensile strains are only reached during extreme joint rotations or direct pressure, their role in normal proprioception can be considered to be limited.

Function

As noted above, joint receptors are considered to primarily encode changes in joint angle at the extremes

of angular excursion. However, given that some joint afferents can encode joint rotation throughout the physiological range [2,6] they may play a role in proprioception when inputs from muscle and skin cannot contribute [9].

Pathology

Loss of joint afferent input is not important; proprioceptive acuity is not greatly affected when people are fitted with prosthetic joints [10].

References

1. Burgess PR, Clark FJ (1969) Characteristics of knee joint receptors in the cat. *J Physiol* 203:317–333
2. Burke D, Gandevia SC, Macefield G (1988) Responses to passive movement of receptors in joint, skin and muscle of the human hand. *J Physiol* 402:347–361
3. Macefield G, Gandevia SC, Burke D (1990) Perceptual responses to microstimulation of single afferents innervating joints, muscles and skin of the human hand. *J Physiol* 429:113–129
4. Edin BB (1990) Finger joint movement sensitivity of non-cutaneous mechanoreceptor afferents in the human radial nerve. *Exp Brain Res* 82:417–422
5. Eklund G, Skogland S (1960) On the specificity of the Ruffini like joint receptors. *Acta Physiol Scand* 49:184–191
6. Ferrell WR (1980) The adequacy of stretch receptors in the cat knee joint for signalling joint angle throughout a full range of movement. *J Physiol* 199:85–99
7. Grigg P, Hoffman AH (1996) Stretch-sensitive afferent neurones in cat knee joint capsule – sensitivity to axial and compression stresses and strains. *J Neurophysiol* 75:1871–1877
8. Gandevia SC, McCloskey DI (1976) Joint sense, muscle sense, and their combination as position sense, measured at the distal interphalangeal joint of the middle finger. *J Physiol* 260:387–407
9. Ferrell WR, Gandevia SC, McCloskey DI (1987) The role of joint receptors in human kinaesthesia when intramuscular receptors cannot contribute. *J Physiol* 386:63–71
10. Cross MJ, McCloskey DI (1973) Position sense following surgical removal of joints in man. *Brain Res* 55:443–445

Proprioception: Roles of Muscle Receptors

UWE PROSKE

Department of Physiology, Monash University,
Melbourne, VIC, Australia

Synonyms

Kinaesthesia; Proprioception

Definition

When limbs are moved, under circumstances where vision cannot be used to monitor the movements, there is a quite accurate sense of where the limbs are in space and whether they are moving or not. This is the ►kinesthetic or the ►proprioceptive sense [1][9].

The neural basis of ►kinesthesia and ►proprioception has been the subject of debate for many years. In the mid nineteenth century it was believed that sensations arising from movements produced by contracting muscles were associated with the motor commands that produced the movements – a “sensation of innervation.” This view was not shared by Sherrington [2] who believed that the kinesthetic sense arose from afferent signals generated in the muscles themselves. Interestingly, the debate about the central and peripheral origin of the kinesthetic sense has not entirely subsided to the present day.

During most of the twentieth century it was believed that ►kinesthetic sensibility was provided predominantly by peripheral signals, although some uncertainty persisted over what kinds of receptors were involved. At one stage it was thought that joint receptors were the main source of input. This idea has not been laid to rest and in recent years, for some joints, contributions from joint receptors [3] as well as skin receptors [4] have been emphasized.

The experiments of Goodwin et al. [5] provided the first direct evidence for a role of a peripheral signal of muscle origin in ►proprioception when they described illusions of both forearm position and movement during 100 Hz vibration of elbow flexor muscles. They concluded that muscle spindles were the principal ►kinesthetic receptor.

Characteristics

Higher Level Structures

A difficulty with muscle receptors as the ►kinesthetic sensors was that until the second half of the twentieth century it remained uncertain whether muscle afferents had access to the cerebral cortex. It is generally accepted that a cortical projection is a necessary prerequisite for access by sensory receptors to consciousness. In the event, it was shown that both spindle Group I afferents (primary muscle spindle endings) and Group II afferents (secondary muscle spindle endings) projected to areas 3a and 4 of somatosensory cortex [6].

Lower Level Structures

The illusions reported by Goodwin et al. [5] were of both position and movement, although vibration at 100 Hz produced principally a movement illusion. When vibration frequency was reduced to 20–40 Hz, the illusion faded from one of movement to one of limb position [7].

Animal studies had demonstrated that the primary endings of spindles had both a dynamic length sensitivity and a static length sensitivity [8]. Furthermore, primary endings were very sensitive to high frequency muscle vibration. It was therefore inferred that the movement illusions experienced during high frequency vibration were the result of signals generated by primary endings.

Secondary endings had no dynamic sensitivity but they responded with maintained changes in discharge during changes in muscle length. They responded only to low frequency vibration. It was concluded that spindle primary endings signaled both movement and position information, while spindle secondary endings contributed only positional information.

Lower Level Processes

Since muscle spindles are stretch receptors, whenever a muscle was stretched during movement of a limb, signals would be generated in both primary and secondary endings. A proportional relationship could be described between the size and rate of stretch and the dynamic and static components of spindle discharge [8]. All of this related to responses of spindles during length changes in the passive muscle. It was known that during a graded voluntary contraction, the ►fusimotor neurons to muscle spindles were ►co-activated [10]. So impulses can be generated in spindles by two fundamentally different processes, stretch and intrafusal contraction.

Higher Level Processes

According to the ►hypothesis that kinesthesia represents two distinct senses, the sense of position and the sense of movement, there is some evidence that central projection sites for dynamic and static spindle signals are separate [6]. Further processing of spindle information must take place to distinguish between ►fusimotor evoked spindle activity (reafference) and muscle stretch evoked activity (exafference). A central subtraction process was postulated to take place [11]. According to this scheme, the motor command goes to both alpha and gamma motoneurons as part of the ►co-activation strategy. Gamma-evoked impulses are subtracted from the total spindle signal to extract movement and position related components. It means that spindles could provide this information at all levels of voluntary activation [7].

Process Regulation

At the present time, we know little about the central processes and their regulation in the generation of ►kinesthetic sensations. Signals from area 3a (dynamic) and area 4 (static) must combine with exafferent information to produce the felt sensation. Where this takes place remains to be shown.

Function

The ►**kinesthetic** sense, making reference to a central map, allows us to locate the body and body segments in space, in the absence of vision. It also provides us with information about movement of the body. Since in everyday life many of our movements are carried out without visual guidance, the ►**kinesthetic** sense is important for normal motor activities.

Pathology

An indication of the importance of ►**kinesthesia** and ►**proprioception** for motor control is provided by subjects with a large fiber sensory neuropathy. These subjects carry out all activities under close visual control. In the absence of vision they exhibit large errors in ►**kinesthetic** tests and they are unaware of obstacles encountered during movements, unless they can see them [1].

►**Large-Fiber Sensory Neuropathy: Effect on Proprioception**

References

1. McCloskey DI (1978) Kinesthetic sensibility. *Physiol Rev* 58:763–820
2. Sherrington CS (1906) On the proprioceptive system, specially in its reflex aspects. *Brain* 29:467–482
3. Ferrell WR, Gandevia SC, McCloskey DI (1987) The role of joint receptors in human kinaesthesia when intramuscular receptors cannot contribute. *J Physiol* 386:63–71
4. Collins DF, Refshange KM, Todd G, Gandevia SC (2005) Cutaneous receptors contribute to kinesthesia at the index finger, elbow and knee. *J Neurophysiol* 94:1699–1706
5. Goodwin GM, McCloskey DI, Matthews PBC (1972) The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain* 95:705–748
6. Hore J, Preston JB, Cheney PD (1976) Responses of cortical neurons (areas 3a and 4) to ramp stretch of hindlimb muscles in the baboon. *J Neurophysiol* 39:484–500
7. McCloskey DI (1973) Differences between the senses of movement and position shown by the effects of loading and vibration of muscles in man. *Brain Res* 61:119–131
8. Matthews PBC (1972) Mammalian muscle receptors and their central actions. Arnold, London
9. Proske U (2006) Kinesthesia: the role of muscle receptors. *Muscle Nerve* 34:545–558
10. Vallbo AB (1974) Human muscle spindle discharge during isometric voluntary contractions. Amplitude relations between spindle frequency and torque. *Acta Physiol Scand* 90:319–336
11. McCloskey DI, Gandevia SC, Potter EK, Colebatch JG (1983) Muscle sense and effort: motor commands and judgements about muscular contractions. In: Desmedt JE (ed) *Motor control mechanisms in health and disease*. Raven, New York

Proprioceptor

Definition

Sensory receptor providing information about the mechanical state of the body.

- Proprioception
- Sensory Systems

Pro-Saccades

Definition

- Oculomotor Control
- Saccade, Saccadic Eye Movement

Prosencephalon

Definition

Forebrain. Anterior part of the brain. Composed of telencephalon and diencephalon.

- Evolution and Embryological Development of the Forebrain
- General CNS

Prosomere

Definition

Transverse, segmental divisions of the forebrain.

- Evolution and Embryological Development of Forebrain

Prosopagnosia

Definition

- Visual Neuropsychology

Prospective Monitoring

Definition

Prospective monitoring is defined as metacognitive experiences that on the basis of evaluation of the current states of memory and learning, one adjust one's behaviors (e.g., by adaptively modifying and/or changing currently inadequate learning strategies and figuring out new strategies), so as to prepare for achieving learning goals.

►Metacognition

Prospero: Protein Localization in Neuroblasts

XIAOHANG YANG

Institute of Molecular and Cell Biology,
Agency for Science, Technology and Research,
Proteos, Singapore

Definition

Prospero belongs to a unique group of proteins that are enriched in either the apical or basal cell cortex, just under the plasma membrane, of dividing neuroblasts. The asymmetric cortical localization of Prospero protein is controlled by a sophisticated ►[asymmetric cell division](#) mechanism that secures the exclusive

segregation of Prospero to the future ►[ganglion mother cell](#) during mitosis.

Characteristics

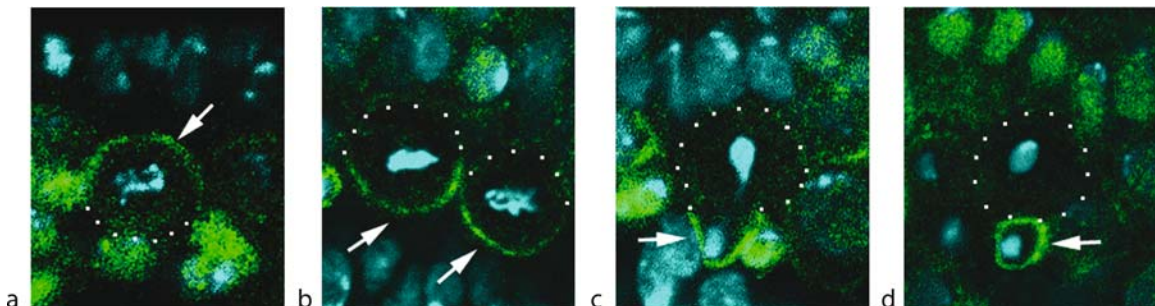
The *Drosophila* embryonic central nervous system (CNS) is derived from an array of approximately 30 unique types of neuroblast. The highly diversified neurons and supporting cells in the CNS are the direct progenies of ganglion mother cells produced by neuroblast asymmetric divisions. The *Drosophila* gene *prospero* (*pros*) is required for the generation of the ganglion mother cell.

pros [1] was identified in the early 1990s and named after the protagonist in *The Tempest*, a play by William Shakespeare. *pros* is located on the right arm of the third chromosome (86E2–86E4) and encodes three slightly varied large polypeptides (1535, 1403 and 1374 aa) due to alternative splicing. The Pros protein is a divergent homeodomain transcription factor that acts as a switch between self-renewal or terminal differentiation of a neural precursor cell. *pros* is evolutionally conserved and vertebrate homologs of *pros*, *Prox1*, have been identified in human, mouse, zebrafish and frog.

During early *Drosophila* embryonic neurogenesis, neuroblasts delaminate from the neuroectoderm and divide asymmetrically along the apicobasal axis to produce one large and one small daughter cell. The size difference between the two daughters is so prominent that it appears as if the small daughter buds off from the basal cortex of the telophase neuroblast (Fig. 1c).

The large apical daughter cell remains as the neuroblast and continues to divide asymmetrically. The small basal cell adopts the ganglion mother ►[cell fate](#) and divides terminally to make either two neurons or glial cells.

P



Prospero: Protein Localization in Neuroblasts. Figure 1 Confocal images of cell cycle-dependent asymmetric distribution of Pros protein in mitotic neuroblasts. Embryos at developmental stage 10 were stained with anti-Pros (green) and ToPro3 (chromosomes, cyan). At late interphase or early prophase, Pros protein is transiently enriched in the apical cortex and forms an apical crescent (Panel a, arrow). Starting from late prophase, Pros is relocated to the basal cortex and remains basal (Panel b, arrows; late prophase and metaphase) throughout the rest of mitosis. At telophase, Pros protein is sequestered into the future ganglion mother cell (Panel c, arrow). After cytokinesis, Pros protein is exclusively inherited by the ganglion mother cell (Panel d, arrow) and translocated into the nucleus later. Apical is up. Neuroblast cell bodies are outlined with white dots.

Pros protein is made in neuroblasts and its cellular distribution is tightly regulated by the cell cycle [1]. Anti-Pros immunofluorescence staining shows that Pros protein transiently enriches in the apical cortex (membrane-associated or “apical crescent”) (Fig. 1a) in late interphase and early prophase neuroblasts. Starting from late prophase, Pros is relocated to the basal cortex of mitotic neuroblasts and remains basal (“basal crescent,” Fig. 1b) throughout the rest of mitosis. In telophase, Pros protein is sequestered into the future ganglion mother cell (Fig. 1c). After cytokinesis, Pros protein is exclusively inherited by the ganglion mother cell (Fig. 1d). In newly formed ganglion mother cells, Pros is cortical (membrane-associated, Fig. 1d) and is translocated into the nucleus later, which is essential for its function. The membrane-associated form of Pros is highly phosphorylated and its translocation to the nucleus requires dephosphorylation [2]. Interestingly, *pros* mRNA exhibits similar asymmetric cellular localization patterns in mitotic neuroblasts and gets sequestered into ganglion mother cells [3].

Pros protein appears to act as a master player (reminiscent of Prospero who has the magic power in *The Tempest*) that controls the ganglion mother cell fate. In the absence of Pros, or failure to translocate Pros to the nucleus, the smaller daughter cell fails to adopt the ganglion mother cell fate and does not produce proper neurons. Thus, Pros is also called a “cell fate determinant.” Another well studied cell fate determinant in neuroblast asymmetric division is Numb [4], which exhibits similar asymmetric basal localization and exclusive segregation into future ganglion mother cells as Pros. Numb antagonizes the Notch signaling pathway.

A number of protein complexes are involved in regulating Pros asymmetric localization in mitotic neuroblasts [5]. Proteins such as Bazooka (Baz), DaPKC, Par6, Inscuteable (Insc), Partner of Insc and the α -subunit of trimeric G-protein, as well as Locomotion defects, co-localize to the apical cortex of mitotic neuroblasts from late interphase and form a functional complex (apical complex). This apically localized complex exhibits three major functions: (i) regulating the basal localization of cell fate **determinants** such as Pros and Numb; (ii) re-orientating the mitotic spindle along the apicobasal axis by metaphase; and (iii) generating an asymmetric spindle (the apical half of the spindle arm is much longer than that of the basal half) which is responsible for the distinct cell size difference between the two daughters. Loss of function of any single protein (for example, in *baz* or *insc* mutants) from the apical complex usually causes mislocalization (randomized Pros crescent position) of Pros protein in early (prior to anaphase) mitotic neuroblasts. However, starting in anaphase, Pros protein in the majority of these mutant

neuroblasts is redistributed as a crescent to the cell cortex where the future **ganglion mother cell** buds off. This redeployment of Pros protein late in mitosis in mutant neuroblasts has been referred to as “telophase rescue.”

The asymmetric localization of Pros in mitotic neuroblasts also depends on a protein called Miranda (Mira) [6], which was named after Prospero’s daughter who went into exile with him in *The Tempest*. In mitotic neuroblasts, Mira binds to Pros and functions as an adaptor protein for Pros asymmetric cortical distribution. In the absence of Mira, Pros loses its asymmetric localization and becomes cytoplasmic.

The cell-cycle dependent translocation of Pros protein from apical to basal cortex is regulated by the Snail family proteins of Zn-finger transcription factors Snail (Sna), Escargot (Esg) and Worniu (Wor) [5]. The members of the Snail family share homologous sequences and exhibit redundant functions. In the absence of all three Snail family proteins, two major players of the apical complex in the embryonic CNS, Baz and Insc, are down-regulated in the segmented CNS but not the brain. In these *snail* triple-mutant (*esg wor sna*) embryos, Pros protein remains tethered to its apical position and does not relocate late in mitosis to the basal cortex from where the future ganglion mother cells bud off. Since these small daughter cells do not inherit Pros, they do not adopt the ganglion mother cell fate. These observations indicate that in addition to the absence of Baz and Insc, the compensatory telophase rescue mechanism is also defective in *snail* triple-mutant (*esg wor sna*) neuroblasts. The detailed mechanism of telophase rescue remains largely unknown. A recent study of telophase rescue has indicated that two *Drosophila* homologs of mammalian TNF/TNFR molecules, Eiger and DTRAF1, are involved in Pros protein telophase rescue [7]. Interestingly, Numb telophase rescue requires neither Eiger nor DTRAF1, which suggests that a different pathway is involved.

Two tumor-suppressor genes, *lethal giant larvae* (*lgl*) and *discs large* (*dlg*), are also involved in the proper basal localization of Pros in dividing neuroblasts [8,9]. In contrast to its asymmetric localization to either the apical or basal cortex in wild type neuroblasts, in the absence of Lgl/Dlg Pros protein is evenly distributed in the cortex and is heavily associated with the mitotic spindle. It has been suggested that Lgl/Dlg may act in a secretory pathway involved in the basal intracellular translocation of Pros. The asymmetric basal localization of Pros protein also depends on the actin cytoskeleton, but not the microtubule structures inside cells. Disruption of the actin cytoskeleton results in loss of Pros from the membrane.

It appears that Pros asymmetric localization is only observed at embryonic stages. During late nervous system development, the asymmetric localization and

segregation mechanism do not seem to play a major role in Pros function and the conventional transcription/translation regulation mechanism prevails. For example, in the 3rd instar larval brain, Pros protein is expressed only in ganglion mother cells and not in neuroblasts, although Mira remains asymmetrically localized in mitotic larval neuroblasts and is exclusively partitioned into ganglion mother cells at telophase. Another example is the development of the adult external sensory organ. Pros protein is cytoplasmic in dividing sensory organ precursor cells and distributes equally to two daughter cells after cytokinesis [10]. Later the Pros protein level is down-regulated in one of the daughter cell (IIa), which divides to produce a hair and a socket. The daughter cell maintaining Pros protein (IIb) produces a neuron and a glial cell.

In summary, the cell fate determinant Pros protein is made in the mother cell (neuroblast) and only functions as a transcription factor in the nucleus of one of the two daughter cells (ganglion mother cell). The cell cycle-dependent asymmetric distribution of Pros protein during mitosis is a critical mechanism employed by dividing neuroblasts to secure the exclusive segregation of this protein to the ganglion mother cells. In vertebrates, it is not known whether Prox1 is involved in asymmetric divisions. Prox1 knock-out mice show embryonic lethality with impaired development of the lens, lymphatic system, liver and pancreas.

References

1. Fuerstenberg S, Broadus J, Doe CQ (1998) Asymmetry and cell fate in the *Drosophila* embryonic CNS. *Int J Dev Biol* 42:379–383
2. Srinivasan S, Peng CY, Nair S, Skeath J, Spana E, Doe CQ (1998) Biochemical analysis of Prospero protein during asymmetric cell division: cortical Prospero is highly phosphorylated relative to nuclear Prospero *Dev Biol* 204:478–487
3. Li P, Yang X, Wasser M, Cai Y, Chia W (1997) Inscutable and Staufan are required for the asymmetric localisation and segregation of Prospero RNA during *Drosophila* neuroblast cell divisions. *Cell* 90:437–447
4. Knoblich JA, Jan LY, Jan YN (1995) Asymmetric segregation of numb and prospero during cell division. *Nature* 377:624–627
5. Chia W, Yang X (2002) Asymmetric division of *Drosophila* neural progenitors. *Curr Opin Genet and Dev* 12:459–464
6. Jan YN, Jan LY (1998) Asymmetric cell division. *Nature* 392:775–778
7. Wang H, Cai Y, Chia W, Yang (2006) *Drosophila* homologs of mammalian TNF/TNFR-related molecules regulate segregation of Miranda/Prospero in neuroblasts. *EMBO J* 25:5783–5793
8. Peng CY, Manning L, Albertson R, Doe CQ (2000) The tumour-suppressor genes *lgl* and *dlg* regulate basal protein targeting in *Drosophila* neuroblasts. *Nature* 408:596–600
9. Ohshiro T, Yagami T, Zhang C, Matsuzaki F (2000) Role of cortical tumour-suppressor proteins in asymmetric division of *Drosophila* neuroblast. *Nature* 408:593–596
10. Manning L, Doe CQ (1999) Prospero distinguishes sibling cell fate without asymmetric localization in the *Drosophila* adult external sense organ lineage. *Development* 126:2063–2071

Prostaglandins

Definition

A group of hormone-like substance derived from arachidonic acid, which participate in a wide range of neuronal and organismal functions.

Prosthesis

Definition

An artificial body part.

► Joints

► Measurement Techniques (Pressure)

Proteases

Definition

Proteases are enzymes that break down other proteins in a cell. Normally, proteases are carefully regulated. If unregulated, severe cell damage and death can occur.

Proteasome

Definition

Proteasome in eukaryotes, proteasomes are large nuclear and cytoplasmic protein complexes that proteolytically degrade proteins.

Protective Autoimmunity

MICHAL SCHWARTZ, JONATHAN KIPNIS
The Weizmann Institute of Science, Rehovot, Israel

Synonyms

Immune based-self maintenance, repair and renewal

Definition

Immune response recognizing auto-antigens that contribute to maintenance, protection, repair and renewal of the relevant tissue; so far proven with respect to the central nervous system.

Characteristics

Description

As a result of tissue injury, physiological compounds flood the body in toxic amounts. ►T cells (T lymphocytes) directed to self-antigens serve as the fighting force against these self-derived threatening factors (“the ‘enemy within’”) [1,2], much as the classical immune response fights invading enemies, such as microbes.

T-cell specificity for self-antigens (►autoimmunity) is required for homing of the T cells to the autoantigen-populated site of damage and their activation there [5]. Following activation by their relevant antigens, the T-cell effect is independent of both antigen specificity and the existing toxicity. These “►autoimmune T cells,” via secreted factors such as cytokines, activate the local ►microglia (brain-resident immune cells) to support neuronal survival and repair [2].

Background

Damage to the central nervous system (CNS) results in irreversible functional loss that is often more extensive than would be expected from the severity of the primary insult [1]. This heightened impairment results from the inevitable degeneration of neurons that sustained the primary injury, as well as from failure of the tissue to withstand the self-perpetuating process of damage that spreads to neighboring neurons. The latter is due to a pathological disruption in homeostasis caused by self-compounds in concentrations that are beyond the buffering capacity of the tissue. In addition, the ability of CNS tissue to tolerate a defense mechanism mediated by its resident immune cells (microglia) is poor; thus, unless tightly controlled, microglial activation is itself likely to exacerbate the damaging conditions rather than help the tissue to withstand them. Poor recovery of the CNS is therefore a reflection of (i) the limited ability to regrow new fibers from cell bodies with damaged axons (regeneration), (ii) failure of the CNS to tolerate adverse conditions, including those caused by ineffectual

attempts at repair, and (iii) the limited capacity of the adult CNS for spontaneous ►neurogenesis (cell renewal). T cell-based protective autoimmunity can be viewed as a means of controlling the brain’s microglia-based system of self-defense in a way that the brain can tolerate.

That the effect of the ►immune system on CNS repair processes might be beneficial was not considered a possibility until the studies done by the Michal Schwartz group at the Weizmann Institute of Science in 1998 [3]. Up to that time, the consensus was that the healthy CNS is refractory to immune cells, and that the successful infiltration of immune cells into the damaged CNS would result in CNS malfunction and should therefore be minimized. Schwartz and her group discovered that – contrary to the traditional dogma – immune cells are pivotal for CNS repair [1,3]. T cells control the microglial response by producing growth factors and cytokines that empower the microglia infiltrating blood-borne macrophages to buffer the injury-induced toxicity [2], thereby avoiding overwhelming damage to neighboring cells. Thus, by acting as a well-controlled link between the damaged CNS and the healing immune system, suitably activated microglia/macrophages can carry out defensive tasks even in a tissue as fragile as the CNS [4].

Contrary to common wisdom, Schwartz’s group suggested that protection, repair, and recovery after a CNS insult necessitate an immune response, but that the response produced is often too weak (and requires boosting) or inappropriate (and in need of modulation and rigorous control); in both cases the resulting modification must be one that the CNS can safely tolerate [4]. In rats or mice devoid of the ability to manifest an adaptive (T cell-mediated) response to CNS injury, the post-injury loss of neural tissue is significantly increased. Moreover, immunization of injured animals with self-antigens, a procedure that boosts accumulation of self-reactive (autoimmune) T cells at the site of injury, decreases neuronal cell death [5]. This phenomenon of ►neuroprotection mediated by autoimmune T cells residing at the site of injury, or “protective autoimmunity,” was found to be physiological response to CNS injury that spontaneously occurs but is apparently insufficient for the repair [4].

Quantitative Aspects

Injury to the CNS induces activation of microglia at the damaged site, beginning at the time of injury and reaching a peak 7–10 days later. Astrocytes, however, disappear from the site of injury, as demonstrated by immunohistochemical analysis of glial fibrillary acid protein, an astrocyte marker. Besides activated microglia, the injury site is also populated by T cells and infiltrating blood-borne monocytes. Their accumulation

starts immediately after the injury, reaches a peak 7–10 days later, and resolves itself by 2–3 weeks following the injury. A well-synchronized response in terms of amount, time and location is pivotal for the repair. Lately protective autoimmunity has been extended to include brain plasticity, not only in disease but also in health. Neurogenesis and spatial learning/memory capabilities were found to be dependant on the availability of T cells recognizing CNS antigens [6].

Higher-Level Structures

T cells that participate in the healing process within the injured CNS are part of the adaptive arm of the immune system. The site of the insult determines the specificity of the T cells needed for protection and repair. In the case of injuries to white matter, the protective T cells must be reactive to antigens associated with CNS myelin whereas after gray matter injuries, the protective T cells are specific to other proteins that are abundantly expressed at the injury site.

Lower-Level Components

Upon reactivation by encountering their specific antigens at the site of injury, the T cells can produce a variety of soluble proteins that are required for normal neuronal function. These include nerve growth factor, brain-derived neurotrophic factor, glial cell-derived neurotrophic factor, and others [7].

Anatomy and Physiology of Regulation

According to the concept of protective autoimmunity, autoimmune T cells in healthy individuals exist in a state that represents a compromise between the need for autoimmune protection and the risk of autoimmune disease. Schwartz's group discovered that a subpopulation of T cells, identified as the naturally occurring regulatory CD4 + CD25 + T cells (Treg cells), constitutively suppressed the activity of autoimmune T cells, and that this population is itself regulated (i.e. the suppression can be abolished or at least weakened) by brain-derived compounds such as the stress-related neurotransmitter dopamine [5].

The Regulatory Process

Naturally occurring Treg cells exert tight control over circulating autoimmune T cells, so that the latter normally exist in a state often described by immunologists as "nonresponsiveness." Treg cells are produced in the thymus and are released to the periphery, where they suppress the activity of autoimmune T cells. Depletion of Treg cells predisposes animals to the spontaneous development of autoimmune diseases. Animals depleted of Treg cells also demonstrate more

efficient rejection of tumors, because their autoimmune Lately protective autoimmunity has been extended to include brain plasticity, not only in disease but also in health. Neurogenesis and spatial learning/memory capabilities were found to be dependant on the availability of T cells recognizing CNS antigens [insert ref ziv et al] [6] T cells can be more easily activated [15]. In line with findings on cancer rejection, depletion of the Treg cell subpopulation enhances the animals' ability to withstand conditions of CNS neurodegeneration [5]. Thus, endogenous compounds such as dopamine, because of their ability to attenuate the activity of the Treg cells, might be useful as potential components of neuroprotective therapies.

Pathology

After an injury, the damaged CNS tissue becomes accessible to immune cells. Although the post-injury inflammatory process that is mediated by self-reactive T cells is a protective physiological response, these autoimmune T cells appear to include the very cells that can also induce experimental autoimmune encephalomyelitis (EAE), an animal model for the autoimmune disease, multiple sclerosis [8]. Therefore, proper regulation is critical if the autoimmune response is to protect the organism from injury-associated damage without the concomitant induction of another kind of pathology, namely autoimmune disease [9].

Therapy

The following immune-based therapies for CNS repair are currently under investigation:

- *T cell-based therapeutic vaccination:* This experimental treatment involves the boosting of T cells directed against weak agonists of self-antigens that cross-react with antigens residing at a site of stress or disease. The risk of autoimmune disease is avoidable by using weak agonists that exhibit only partial cross-reactivity with their relevant self-antigen. One such antigen is glatiramer acetate, also known as copolymer 1 (Cop-1), a synthetic copolymer composed of four amino acids (glutamate, lysine, alanine, and tyrosine). Immunization with Cop-1 was found to be neuroprotective in several models of CNS injury and neurodegenerative disorders [7]. Another possible way to boost autoimmune T cells is through the use of altered peptide ligands. An altered dominant peptide of myelin basic protein (MBP) that does not induce EAE upon immunization was found to be significantly neuroprotective in a rodent model of spinal cord injury [10].
- *Weakening of the activity of ►regulatory T cells:* Neuroprotection is enhanced in mice depleted of Treg cells [5]. In human subjects such depletion is

impossible, as most of these cells are located in lymph nodes, and there is no known way to selectively remove them. Therefore, compounds that can selectively weaken the suppressive activity of Treg cells are potential candidates for therapy. One such compound is the neurotransmitter dopamine, which alleviates the suppressive activity of naturally occurring Treg cells. Injection of dopamine or dopamine-receptor type-1 agonists after CNS injury was found to be neuroprotective [5]. An additional compound found to be effective in modulating T reg is a copolymer of glutamate tyrosine, poly YE, show to be effective in stroke [5].

- **Autologous macrophages:** These cells constitute the basis of an immune-based cell therapy for spinal cord repair. Depending on their environmental conditions, cells of the macrophage lineage can acquire either the type of activation appropriate for fighting off invading microorganisms, or – activation leading to tissue maintenance and repair. Schwartz's group discovered that macrophages with the characteristic features of antigen-presenting cells can facilitate CNS repair [3]. Once activated by autologous tissue such as skin, these macrophages produce cytokines and neurotrophic factors, but not tumor necrosis factor- α or other cytotoxic agents. In a therapy currently under development, macrophages are prepared from the patient's own blood, activated on the patient's own skin in such a way that they adopt a repair-promoting phenotype, and reintroduced into the margin of the lesion site at the specific time and dosing, facilitates repair. Such macrophages are reminiscent of the ones recruited by immunization with CNS self-antigen following spinal cord injury [11].
- **Dendritic cells:** Bone marrow-derived dendritic cells are professional antigen-presenting cells, which can be loaded with antigens and used to treat the acutely injured CNS. Dendritic cells prepared from autologous blood and loaded with relevant CNS antigens, can (like macrophage therapy) be applied locally to the severed spinal cord, or administered systemically as a vaccination [12].

Concluding Remarks

The immune system is the body's primary source of defense against danger and remedial assistance in the event of injury. The CNS, however, was long thought to have relinquished its claim on the immune system for such help, possibly as an evolutionary trade-off that protected its extraordinarily complex neural network from harmful immune (inflammatory) intervention. Similarly, immune cells directed against self-antigens, traditionally viewed as autoaggressors causing autoimmune disease, acquired an unfavorable reputation as an

outcome of immune system malfunction. The studies described here, as well as studies from many other laboratories, provide persuasive evidence that the negative reputation of the immune system vis-à-vis the CNS is undeserved. Nevertheless, spontaneous activation of the CNS-resident microglia is often not sufficiently effective. Thus, additional assistance is needed from cells that constitute the adaptive arm of peripheral immunity, namely T cells specific to CNS self-antigens. Based on this concept, several approaches can be translated into workable therapies. The treatment of choice will ultimately be based on safety, feasibility, and efficacy, and the specific indication.

References

1. Moalem G et al. (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med* 5:49–55
2. Schwartz M, Shaked I, Fisher J, Mizrahi T, Schori H (2003) Protective autoimmunity against the enemy within: fighting glutamate toxicity. *Trends Neurosci* 26:297–302
3. Rapalino O et al. (1998) Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nat Med* 4:814–821
4. Yoles E et al. (2001) Protective autoimmunity is a physiological response to CNS trauma. *J Neurosci* 21:3740–3748
5. Kipnis J et al. (2004) Dopamine, through the extracellular signal-regulated kinase pathway, downregulates CD4 + CD25 + regulatory T-cell activity: implications for neurodegeneration. *J Neurosci* 24:6133–6143
6. Ziv Y et al. (2006) Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nat Neurosci* 9(2):268–275
7. Kipnis J et al. (2000) T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc Natl Acad Sci USA* 97:7446–7451
8. Sakaguchi S et al. (2001) Immunologic tolerance maintained by CD25 + CD4 + regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol Rev* 182:18–32
9. Schwartz M, Kipnis J (2002) Autoimmunity on alert: naturally occurring regulatory CD4(+)CD25(+) T cells as part of the evolutionary compromise between a 'need' and a 'risk'. *Trends Immunol* 23:530–534
10. Hauben E et al. (2001) Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents Complete paralysis while avoiding autoimmune disease. *J Clin Invest* 108:591–599
11. Rossignol S, Schwob M, Schwartz M, Fehlings MG (2007) Spinal cord injury: Time to move? *J Neurosci* 27(44):11782–11792
12. Hauben E et al. (2003) Vaccination with dendritic cells pulsed with peptides of myelin basic protein promotes functional recovery from spinal cord injury. *J Neurosci* 23:8808–8819

Protein Kinase A (PKA)

Definition

Also known as cAMP-dependent protein kinase. A family of protein kinases whose activity are dependent on the level of cAMP in the cell.

Protein Kinase C (PKC)

Definition

An enzyme that exists in many different forms, which are central to many signal transduction mechanisms in brain cells.

Protein Phosphatase 1, PP-1

►Protein Serine/Threonine Phosphatases in the Nervous System

Protein Phosphatase 2A, PP-2A

►Protein Serine/Threonine Phosphatases in the Nervous System

Protein Phosphatase 2B, PP-2B

►Protein Serine/Threonine Phosphatases in the Nervous System

Protein Serine/Threonine Phosphatases in the Nervous System

QIN YAN^{1,2}, YING-WEI MAO³, DAVID W. LI^{1,2,4}

¹Department of Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

²Key Laboratory of Protein Chemistry and Developmental Biology of National Education Ministry of China, College of Life Sciences, Hunan Normal University, Changsha, Hunan, China

³Howard Hughes Medical Institute, Massachusetts Institute of Technology, Boston, MA, USA

⁴Department of Ophthalmology and Visual Sciences, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Synonyms

Protein Phosphatase 1, PP-1; Protein Phosphatase 2A, PP-2A; Protein Phosphatase 2B, PP-2B

Definition

Protein Serine/threonine phosphatases are a family of protein enzymes, which specifically remove the phosphate group from the serine or threonine residues of the substrate proteins. These phosphatases termed PPPs include ►PP-1, ►PP-2A, ►PP-2B, ►PP-2C, PP-4, PP-5, PP-6 and PP-7.

Characteristics

The reversible ►phosphorylation and ►dephosphorylation of proteins at the serine, threonine and tyrosine residues play fundamental roles in mediating different signaling transduction pathways and thus act as a major mechanism to regulate eukaryotic cellular events such as gene expression, cell proliferation, differentiation, homeostasis and apoptosis. The two processes executed by ►protein kinases and ►protein phosphatases can trigger conformational changes in regulated proteins that finally alter their biological properties and functions. In this regard, phosphorylation may endow a protein with a favorable conformation for binding by its relative substrates or partners, which in the end brings about some cellular and morphological changes; on the contrary, its dephosphorylated form may possess these features. And at any instant, a protein's specific phosphorylation status is a balanced result between its regulatory kinases and phosphatases.

Genome research has identified 147 genes coding for the catalytic subunits of protein phosphatases. According to differences in substrates, the protein phosphatases can be divided into three groups, including ►protein serine/threonine phosphatases (PPPs), protein ►tyrosine

phosphatases (PTPs), and dual-specific phosphatases (DSPs). On the basis of the selective inhibition of type-1 phosphatases (PP-1) by endogenous inhibitor-1 (►I-1) and inhibitor-2 (►I-2), the PPP family can be further divided into type-1 (PP-1) and type-2 (►PP-2) subgroups and a few minor phosphatases that include PP-4, -5, -6 and -7, although these phosphatases have a broad and overlapping substrate specificity. The PP-1 enzyme is composed of a catalytic subunit and one or more regulatory subunits, and it is hard to distinguish the regulatory subunit from its inhibitor or substrate. The PP-2 subgroup consists of three enzyme members, PP-2A, PP-2B and PP-2C, which can be distinguished by their substrate specificity, subunit number and the specific cations needed for function. For instance, PP-2A can dephosphorylate phosphorylase-a, while PP-2B and PP-2C do not. In addition, calcium is necessary for the function of PP-2B, which is also known as calcineurin. While PP-2A is composed of three subunits and PP-2B two subunits, PP-2C is a monomeric enzyme. In eukaryotes, 98% of dephosphorylation occurs at the serine/threonine residues, and more than 90% of protein ►serine/threonine phosphatase activity is contributed by PP-1 and PP-2A [1].

Protein Phosphorylation in the Nervous System

Based on morphology and physiology, the adult nervous tissue is composed of two main cell types: neurons and glial cells. Neurons transmit high speed nerve signals through depolarization potentials, while glial cells are in direct contact with neurons to provide a basic support. Existing in variable sizes and shapes, neurons are the functional units of the nervous system. All neurons consist of three parts: dendrite, cell body and axon. Dendrites receive information from another cell and transmit information to the cell body. The cell body contains the nucleus, mitochondria and other organelles typical of eukaryotic cells, and processes the neuronal signals for further transduction. The axon sends information away from the cell body. Under normal conditions, glial cells surround neurons to modulate neuronal homeostasis and detoxification, and produce neuronal survival factors. The functions of crucial proteins in the nervous system are modulated by kinases and phosphatases. This essay focuses on the functions of three major protein phosphatases in the nervous system, PP-1, PP-2A and PP-2B.

Protein Phosphatase-1 (PP-1)

Early studies showed that PP-1 accounts for 25–40% of the phosphorylase phosphatase activity in brain crude tissue extracts. In isolated synaptic junctions from rat forebrain, PP-1 accounts for 80% of the membrane-associated phosphatase activity. PP-1 can be inactivated by the inhibitor I-1 when phosphorylated by CAMP-dependent protein kinases, or by the inhibitor I-2 in the

dephosphorylated form. In addition to the ubiquitous I-1 and I-2 inhibitors, brain tissue also contains a unique PP-1 inhibitor, ►DARPP-32, present predominantly in neural tissues. The localization of DARPP-32 is unique, for it is abundant in specific areas of the brain, including the basal ganglia which contains as much as 130 pmol of DARPP-32 per mg protein, but absent from most other tissues. Compared with the basal ganglia, the thalamus and cerebellum contain much less DARPP-32. In brain areas rich in DARPP-32, discrete populations of neurons show particularly high level of expression, such as the D1-receptor dopaminergic neurons, and the Purkinje cells of the cerebellum. The high phosphatase activity of PP-1 in the brain and its co-localization with the cognate inhibitors suggest that PP-1 might serve as an important regulatory enzyme in various neuronal events.

Neurons produce and transduce signals through alternative shifts in membrane potentials, which depend on different ion channels distributed in the plasma membranes. Ion channel activity can be regulated by closely associated kinases or phosphatases, which serves as a key mechanism for orchestrating neuromodulation. PP-1 is responsible for the dephosphorylation and modulation of some neuronal ion channels. In many instances, dephosphorylation is required for channel activity. An exemplary case is the peptide neurotransmitter Phe-Met-Arg-PheNH₂ (FMRFamide) related serotonin-sensitive K⁺ (S-K⁺) channel in Aplysia sensory neurons. Two PP-1 isoforms, with apparent MW of 170,000 and 38,000, were extracted from crude membrane preparations from the Aplysia nervous system. Biochemical and physiological studies suggest that of the two major protein phosphatases, PP-1 and PP-2A, PP-1 is associated preferentially with neuronal membranes and its activity is required for the induction of outward K⁺ currents in Aplysia sensory neurons by FMRFamide [2]. Similarly, in rat brain and cerebellar Purkinje neurons, activation of the calcium-dependent potassium channels (BK channels) by neurotrophin-3 depends on their prior dephosphorylation by PP-1 or PP-2A. In addition, certain protein phosphatases are involved in the function of the nonselective cation channel that drives the after-discharge in Aplysia bag cell neurons. It has been shown that the reversal of the nonselective cation channel after addition of ATP was prevented by the PP inhibitor, ►microcystin-LR.

Various receptors in the nervous system play important roles in mediating signal transduction. Protein phosphatases can modulate the functions of these receptors through dephosphorylation. An example is the regulation of AMPA receptor by PP-1. The filamentous actin binding protein neurabin I (Nrb I) targets PP-1 to specific postsynaptic microdomains, where it can exert critical control over AMPA receptor-mediated synaptic transmission. PP-1 dephosphorylates

AMPA subtype glutamate receptor (GluR) 2 at Ser 880 to stabilize the basal transmission; while with long-term depression (LTD), PP-1 dephosphorylates GluR1 at both serine 845 and serine 831. These results suggest that in response to distinct synaptic activities post-synaptic targeted PP-1 could regulate the synaptic trafficking of specific AMPA receptor subunits [3]. In the western painted turtle, PP-1 or PP-2A dephosphorylates N-methyl-d-aspartate (NMDA) receptors and decreases their activity, which attenuates calcium influx and thus, excitotoxic cell death (ECD), a characteristic of mammalian brain following anoxia.

Physiological modulation of other target molecules by protein serine/threonine phosphatases also plays a role in the nervous system. Neural cell adhesion molecule (NCAM) has important functions during development and maintenance of the nervous system. NCAM 140 and NCAM 180 are transmembrane glycoproteins with large cytoplasmic domains of different lengths. PP-1 and PP-2A bind to both NCAM 140 and NCAM 180, suggesting possible functions of these two protein phosphatases during the development and maintenance of the nervous system. Further, doublecortin (DCX) is a highly phosphorylated protein in migrating neurons, whose mutation causes X-linked lissencephaly (“smooth brain”) and double cortex syndrome in humans. It was reported that PP-1, by recruitment of Neurabin II, dephosphorylates the specific sites in DCX phosphorylated by JNK, which plays an important role in normal neuronal migration [4]. Finally, PP-1 may play an important in regulating brain and eye development. We recently demonstrated that PP-1 acts as a major phosphatase dephosphorylating the transcription factor Pax-6, which is highly expressed in the developing nervous system, and attenuates its transcriptional activity.

Protein Phosphatase-2A (PP-2A)

PP-2A, also known as a polycation-stimulated phosphatase, is very abundant in brain where it is mainly cytosolic and represents 60–75% of the phosphorylase phosphatase activity. The PP-2A core enzyme is composed of a catalytic subunit (C) and a tightly complexed scaffolding subunit A. This core enzyme associates with a regulatory subunit B, whose function is to target the whole enzyme to specific intracellular locations and substrates. There are four subgroups of the B family subunits including B/PR55, B'/PR56/PR61, B''/PR72 and B'''/PR93/PR110. The major function of the ubiquitously expressed PP-2A seems to be related with a wide range of events under both physiological and pathological conditions in the nervous system.

PP-2A is implicated in Alzheimer's disease (AD), a progressive brain disorder that gradually destroys a person's memory and ability to learn, reason and communicate. The major brain abnormalities in patients

with AD include extracellular deposits of beta-amyloid, intraneuronal neurofibrillary lesions, and the massive loss of specific subsets of telencephalic neurons. Dysregulation of the regulatory subunit of **▶PP2A**, B/PR55, has been implicated in AD. Since one of the major functions of the B subunit in PP-2A is to target the whole enzyme to its substrates, its dysregulation might lead to a failure of dephosphorylation of relevant brain proteins and finally AD. Further, researchers have found that the abnormal phosphorylation of paired helical filaments (PHF) tau resulting from the failure of PP-2A and PP-2B may disrupt the microtubule network, impair axonal transport, and compromise the viability of neurons, thereby also contributing to the onset and progression of AD [5]. In the non-diseased nervous system, research at the *Drosophila* neuromuscular junction suggests that the B' regulatory subunit of **▶protein phosphatase 2A** may regulate normal cytoskeletal organization, synaptic growth, and synaptic function.

The physiological function of PP-2A is also being revealed. It was reported that PP-2A is required for the differentiation of pluripotent neural crest (NC) cells into the sympathoadrenal lineage. A moderate activation of cAMP signaling induces both the transcription and activity of the proneural transcription factor Phox2a in NCs, whereas treatment with the **▶organic phosphatase inhibitor**, **▶okadaic acid**, at a concentration (1–10 nM) effective to inhibit PP-2A, suppresses sympathoadrenal lineage development. PP-2A also functions in the mature nervous system. During spinal cord **▶central sensitization**, PP-2A may play an important role in determining the excitability of **▶nociceptive neurons** in the spinal cord by modulating the phosphorylation state of certain critical proteins. For instance, infusion of the phosphatase inhibitor okadaic acid or **▶fostricic**, a specific PP-2A inhibitor, into the **▶subarachnoid space** enhances secondary mechanical **▶hyperalgesia** and **▶allodynia** [6]. In addition, it was observed that blockade of protein phosphatase activity potentiates central sensitization of nociceptive transmission in the spinal cord following capsaicin injection, indicating that PP-2A may be involved in determining the duration of capsaicin-induced central sensitization. Finally, since cyclin G1 and the B' subunits of PP-2A are co-localized in neurons, the function of PP-2A in the nervous system may depend partly on its regulation of cell cycle in neurons [7].

Protein Phosphatase-2B (Calcineurin)

PP-2B belongs to the family of Ca^{2+} /calmodulin-dependent protein phosphatases and it is the only protein phosphatase regulated by a second messenger, Ca^{2+} . Furthermore, PP-2B is highly localized in the central nervous system, especially in those neurons

vulnerable to ischemic and traumatic insults. For these reasons, PP-2B is considered to play important roles in neuron-specific functions.

PP-2B has been extensively studied in nervous tissue. It was first purified as a major calmodulin-binding protein in brain (accounting for up to 1% of the total protein), and later identified as a protein phosphatase. The whole enzyme consists of two subunits, the catalytic and calmodulin-binding subunit calcineurin A, and the calcium binding regulatory subunit calcineurin B. PP-2B is essentially a neuronal protein due to its abundance in brain, where levels are 10–20 times higher than in other tissues. Nevertheless, it is distributed amongst a wide set of tissues in many species from yeast to mammals.

Some ion channels and receptors are regulated by PP-2B. In sympathetic neurons, the M current regulates neuronal excitability. Intracellular application of a preactivated form of PP-2B inhibited the macroscopic M current, while its application to excised inside-out patches reduced high open probability M channel activity. Thus, it is suggested that PP-2B selectively regulates M channel modal gating. PP-2B may also regulate the coupling between G protein and calcium channels in rat sympathetic neurons, as the $\alpha 2$ noradrenergic and somatostatin receptor-induced inhibition of N-type Ca^{2+} channels was greatly reduced by inhibition of PP-2B. Interestingly, PP-2B in some cases may regulate both the function and the expression of a protein. For instance, PP-2B directly regulates type 1 inositol 1, 4, 5-triphosphate receptor (IP3R) function by dephosphorylation on a short-term time scale and IP3R expression over more extended periods.

The physiological functions of PP-2B in the nervous system seem to be quite diverse. On one hand, PP-2B regulates certain signaling transduction pathways in neurons by directly dephosphorylating target protein substrates. An example is its regulation of the NF- κ B pathway in astrocytes of the injured brain. After brain injury a reactive phenotype of astrocytes is triggered which produces inflammatory cytokines and neurotoxic free radicals and leads to brain trauma. Under such circumstances, insulin-like growth factor-I (IGF-I) regulates the NF- κ B pathway by activating PP-2B to dephosphorylate I κ B α , which leads to a stabilization of I κ B α and retention of NF- κ B in the cytosol and hence inhibition of the inflammatory reaction [8].

In other systems, the signal transduction pathways regulated by PP-2B result in the activation of different transcription factor cascades. For instance, in the mammalian nervous system, PP-2B appears to regulate the number of excitatory synapses via myocyte enhancer factor 2 (MEF2). After dephosphorylation and activation by PP-2B, MEF2 promotes the transcription of a set of genes that restricts synapse number.

Alternatively, regulation of other signaling transduction pathways by PP-2B involves the downstream transcription factor NF-AT. In calcium-regulated pathways related to learning and memory process, NF-ATc4/NF-AT3 in hippocampal neurons can be translocated rapidly from the cytoplasm to the nucleus to activate NF-AT-dependent gene transcription in response to electrical activity or potassium depolarization. The PP-2B-mediated translocation is critically dependent on calcium entry through L-type voltage-gated calcium channels. This indicates that PP-2B/NF-AT-mediated gene expression may be involved in the induction of hippocampal synaptic plasticity and memory formation. In addition, the PP-2B/NF-AT pathway is involved in neuronal axon outgrowth, the first step in the formation of neuronal connections. After stimulation by growth factors, PP-2B caused nuclear localization of NF-ATc4 and the activation of NF-AT-mediated gene transcription in cultured primary neurons. Blockade of this pathway prevented axon outgrowth, indicating that PP-2B/NF-AT signaling is required during nervous system development [9]. PP-2B also enhances NGF-induced neurite outgrowth.

The list of roles for PP-2B is ever growing in that PP-2B activity regulates synaptic function. For instance, PP-2B activity is required for three forms of synaptic plasticity in the hippocampus and associative learning in *Caenorhabditis elegans* and also reward-related learning in mice. The importance of PP-2B in synaptic function is illustrated by the fact that conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia [10], and that PP-2B is also implicated in epileptogenesis.

Conclusions

In summary, the protein serine/threonine phosphatases seem to be involved extensively in the regulation of neuronal development, differentiation, physiology and pathogenesis. The unscrambling of the signaling transduction pathways in nervous system would be a feasible solution for the ultimate conquering of various brain diseases such as Alzheimer's disease, epileptogenesis, and schizophrenia. Elucidation of the functional mechanisms of the protein phosphatases in the nervous system will provide a better understanding of neuronal function and brain disease.

Acknowledgments

This work is supported in part by the NIH/NEI grant 1R01EY015765, the startup funds from the University of Nebraska Medical Center, the Changjiang Scholar Team Project Funds from the National Education Ministry of China and the Lotus Scholar Program Funds from Hunan Province Government and Hunan Normal University.

References

1. Cohen P (1989) The structure and regulation of protein phosphatases. *Annu Rev Biochem* 58:453–508
2. Endo S, Critz SD, Byrne JH, Shenolikar S (1995) Protein phosphatase-1 regulates outward K⁺ currents in sensory neurons of *Aplysia californica*. *J Neurochem* 64(4):1833–1840
3. Hu XD, Huang Q, Yang X, Xia H (2007) Differential regulation of AMPA receptor trafficking by neurabin-targeted synaptic protein phosphatase-1 in synaptic transmission and long-term depression in hippocampus. *J Neurosci* 27(17):4674–4686
4. Shmueli A, Gdalyahu A, Sapoznik S, Sapir T, Tsukada M, Reiner O (2006) Site-specific dephosphorylation of doublecortin (DCX) by protein phosphatase 1 (PP1). *Mol Cell Neurosci* 32(1–2):15–26
5. Trojanowski JQ, Lee VM (1995) Phosphorylation of paired helical filament tau in Alzheimer's disease neurofibrillary lesions: focusing on phosphatases. *FASEB J* 9(15):1570–1576
6. Zhang X, Wu J, Fang L, Willis WD (2003) The effects of protein phosphatase inhibitors on nociceptive behavioral responses of rats following intradermal injection of capsaicin. *Pain* 106(3):443–451
7. van Lookeren Campagne M, Okamoto K, Prives C, Gill R (1999) Developmental expression and co-localization of cyclin G1 and the B' subunits of protein phosphatase 2a in neurons. *Brain Res Mol Brain Res* 64(1):1–10
8. Sebastian Pons and Ignacio Torres-Aleman (2000) Insulin-like growth factor-I stimulates dephosphorylation of IyB through the serine phosphatase calcineurin (protein phosphatase 2B). *J Biol Chem* 275(49):38620–38625
9. Graef IA, Wang F, Charron F, Chen L, Neilson J, Tessier-Lavigne M, Crabtree GR (2003) Neurotrophins and netrins require calcineurin/NFAT signaling to stimulate outgrowth of embryonic axons. *Cell* 113(5):657–670
10. Miyakawa T, Leiter LM, Gerber DJ, Gainetdinov RR, Sotnikova TD, Zeng H, Caron MG, Tonegawa S (2003) Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc Natl Acad Sci USA* 100(15):8987–8992

Protein Synthetic Machinery

Definition

The protein synthetic machinery of a eukaryotic cell consists of ribosomes, endoplasmic reticulum (ER) and Golgi apparatus. Proteins destined to stay within the cytoplasm (cytosolic proteins) are synthesized on ribosomes and the product is released into the cytoplasm. Luminal proteins (proteins packaged in vesicles) and integral membrane proteins are synthesized on ribosomes that are docked on the endoplasmic reticulum, and the polypeptide chain is secreted in the lumen of the ER (luminal proteins), or is inserted into the membrane of the ER (integral membrane proteins).

After trafficking through the Golgi apparatus the proteins are either released (secretory proteins), inserted into the cytoplasmic membrane (integral membrane proteins), or stored within vesicles in the cytoplasm (lysosomes).

► Extrasomal Protein Synthesis in Neurons

Protein Tyrosine Kinase

Definition

A protein that contains a domain that acts as a kinase, which transfers a phosphate group from ATP to a tyrosine of a protein.

Protein Zero (P0)

Definition

P0 was identified as the major protein component of Schwann cell myelin. The P0 gene is expressed throughout the Schwann cell lineage, from precursors in embryonic development to myelinating Schwann cells in the adult animal. During development, neurons do not express P0 gene, thus P0 gene expression can be used as an early marker of glial specification in neural crest development. In normal adult nerves, expression of P0 gene and protein is restricted to myelin-forming Schwann cells.

► Myelin

► Schwann Cell

► Schwann Cells in Nerve Regeneration

Proteoglycan

Definition

Proteoglycans are molecules that possess a protein core to which are attached one or more glycosaminoglycan chains at serine residues through a four sugar linker. In chondroitin sulfate proteoglycans the chains are made of repeating glucuronic acid and n-acetyl galactosamine, while in heparan sulfate proteoglycans the two

sugar repeat is glucuronic acid (which may be epimerized to iduronic acid) and n-acetyl glucosamine.

The glycosaminoglycan chains are modified by sulfation at various points on the two sugars. Particularly in heparan sulfates sulfation occurs in patches. The pattern of sulfation defines the charge pattern of the glycan and therefore its binding properties. Chondroitin sulfate proteoglycans often have barrier functions, while heparan sulfate proteoglycans are often found as part of a ternary complex presenting growth factors to their receptors.

Proteomics and the Study of the Nervous System

JENS R. COORSEN^{1,2}

¹Hotchkiss Brain Institute, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

²Chair of Molecular Physiology, School of Medicine, University of Western Sydney, Campbelltown, NSW, Australia

Definition

Proteomics encompasses a number of techniques and approaches. At its simplest, it could be described as the large-scale analysis of the proteins encoded by a given genome, or of those proteins present, at the time of sampling, in a given biological milieu (e.g., tissue/cell extract, bodily fluid, etc). The term, coined by Marc Wilkins and colleagues in 1994, describes a new discipline that has moved forward from genomics to enable a more mechanistic understanding of biological processes and disease states. While the genome provides information regarding the proteins (and mutations) potentially expressed by a specific organism, it does not identify which proteins are locally expressed at a specific time, under specific conditions, nor does it provide information concerning the myriad of potentially critical post-translational modifications that can affect specific aspects of protein localization and function. Furthermore, although assessment of mRNA levels (►transcriptomics) is sometimes used as a surrogate for more detailed protein analyses, this often does not accurately reflect the actual protein complement (e.g., functional players) at the time of sampling. Thus, the definition of proteomics has grown to include not only the presence of an array of proteins in a sample, but also the localization, post-translational modifications, activities, and interactions of these proteins with each other and with other molecules. In many ways, the original approach has spawned a variety of sub-disciplines that might be broadly defined as follows:

Functional proteomics – the tight coupling of quantitative functional assays with detailed protein analyses as a direct route to dissecting molecular mechanisms underlying physiological processes.

Structural proteomics – perhaps most akin to structural biology, with the goal of defining the three dimensional or atomic structure of a protein as a route to understanding functional interactions/mechanism(s) of action within the cellular environment.

Discovery or Clinical proteomics – scanning of ►proteomes to identify alterations that potentially underlie a disease pathway or that could serve as biomarkers for specific clinical conditions. The resulting “catalogues” generally serve as important databases for other ongoing work as well.

Characteristics

What then separates proteomics from more traditional protein biochemistry/physical chemistry and cell physiology? This is generally seen to be a matter of scale, throughput, and automation. Rather than asking about the potential role of a single protein in a specific process, proteomics takes a global or systems approach to the integrated roles of proteins in physiological processes. Thus, as a discipline, proteomics has really arisen from the necessary interactions of protein (bio)chemists, cell physiologists, computer scientists, and engineers. The goal of this inter-disciplinary approach is to enhance the ►resolution and throughput of large-scale protein analysis, while simultaneously reducing any potential user bias in the assessment process. With the introduction of computer-driven automation, robotics, and data analysis, the result has been enhanced reproducibility, sensitivity, higher throughput, more objective analyses of the resulting protein data (particularly via subtractive analysis to identify critical differences between data sets), and the establishment of a myriad of databases, making information sharing one of the more important and successful priorities in proteomics.

Techniques

Until relatively recently, proteomics was almost synonymous with two-dimensional polyacrylamide gel electrophoresis (2DE). Building from earlier work, this technique was introduced in the mid-1970s and immediately revolutionized protein analysis. Proteins are separated by ►isoelectric focusing in the first dimension, according to their ►pI (Isoelectric Point), and in the second dimension according (approximately) to their molecular weight (MW), using sodium dodecyl sulphate polyacrylamide gel electrophoresis ►SDS-PAGE (Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis) [1]. In principle, any physical attribute of a protein can be used to establish a separation/purification strategy; hydrophobicity is another commonly used characteristic to aid in protein isolation. For several

years, identification of specific protein spots could only be done by Western blotting (immunodetection) or Edman degradation. The real revolution in terms of proteomics developing as a discipline was the integration of ► **mass spectrometry** for protein identification. With an appropriately “clean” protein sample (see below), it is now routine to excise a spot of interest from a 2DE gel, digest it with a protease (usually trypsin) or another selective agent (such as cyanogen bromide), and analyze the resulting peptides using a variety of mass spectrometric methods. The simplest analysis is to derive a peptide fingerprint and attempt to identify the protein using computerized searches of available databases; essentially, archived protein sequences are digested *in silico*, and the best matches to the unknown protein identified. This approach has fallen out of favor due to a high rate of false-positives, although with a well-defined genome to search, this can be a useful scanning tool. More effort is now placed in using mass spectrometry for *de novo* protein sequencing and thus definitive protein identifications, as well as for the analysis of post-translational modifications [2].

Within the last several years, non-gel based approaches to large-scale protein resolution have been developed based on a combination of liquid chromatography and mass spectrometry (or other techniques “hyphenated” with mass spectrometry). Basically, a gross protein extract is proteolytically digested to yield a complex peptide mixture and this is then fractionated, generally by sequential cation-exchange and reverse-phase chromatography, and random samples of the separated peptides are then sequenced in a mass spectrometer [3]. Possible protein identifications are then made based on the presence of peptides “unique” to specific proteins. This so-called “shotgun” proteomics approach has proven to be an effective scanning tool. Most recently, additional proteomic applications for mass spectrometry have included analysis directly from tissue samples (“imaging” mass spectrometry); although not of high resolution, this technique does provide direct information on the localization of specific proteins [4].

Pros and Cons

It is probably safe to say that 2DE remains the workhorse of proteomics and the current gold-standard in terms of protein resolution. It certainly remains the only method currently available with the capacity to resolve thousands of proteins in a single run. The major complaint that seems to be leveled against it is that it is “old,” yet it is precisely this maturity that yields analytical power: problems have been identified and effectively addressed; in the case of newer approaches, most problems have likely not even yet been effectively identified. High throughput always comes at a cost; in the case of shotgun methods, information concerning the ► **pI**, MW, and post-translational modifications of

proteins is lost, and the approach requires substantial computing infrastructure. Nonetheless, it is likely an integration of these scanning and higher resolution approaches that will define future proteomic efforts, particularly considering the current pace of developments in mass spectrometry.

Regardless of the analytical approach used, the biggest difficulty in proteomics is that of protein detection. While it is likely that we are currently capable of resolving most proteins, those present at lower abundance (e.g., a few to tens of copies per cell) are not detectable using currently available total protein stains [5]; if a protein of interest is known, it can however be detected by a quantitative, high sensitivity Western blotting protocol [6]. There is currently no simple solution to this general detection problem except to fractionate the sample in some way and thus increase the total protein concentration of a specific fraction prior to analysis. Such prefractionation techniques are currently under intense development, particularly for samples such as plasma and cerebrospinal fluid that are dominated by a few high abundance species that obviate the effective analysis of the rest of the proteome. Such prefractionation can be as simple as lysing a tissue sample or cell pellet and using ultracentrifugation to isolate total soluble and membrane protein fractions that can then be separately resolved [7,8]. A myriad of alternate techniques, including sequential extractions with different detergents and/or solvents, selective precipitation, or immuno-isolation of select components, each resulting in the concentration of certain proteins, are all being used. Notably, care must be taken to avoid potential non-specific alterations to the proteome using these more aggressive approaches. In this regard, it has also been found that 2DE gels can be post-fractionated to further enhance the resolution of this technique [8].

Process

The primary caveat when embarking on any proteomic analysis is cleanliness. In the past, if all that was to be done with a 2DE gel for instance was staining or Western blotting, minor contaminants (most commonly, human skin keratin!) were of little or no consequence. Now however, the goal is to identify specific resolved proteins using mass spectrometry; more often than not, the first painful lesson is to find keratin everywhere, obviating any possible protein identification. All buffers and equipment must be scrupulously clean and maintained as such. The Brain Proteome Project initiative of the Human Proteome Organization is helping to establish criteria for sample handling and analysis (www.hbpp.org).

The goal of proteomics is thus an analysis that accurately represents the underlying biological complexity of the sample at the instant of sampling. Thus, regardless of the analytical technique eventually used to resolve the proteins, there must be a focus on optimal sample handling. All tissue dissections, isolations, and

extractions are done in the presence of broad-spectrum protease, kinase, and phosphatase inhibitors [7,8]. In the case of tissue samples, including brain and spinal cord, we have found that the only way to ensure integrity of the protein complement is to snap freeze the sample at the instant of sampling; subsequent automated frozen disruption effectively powders the sample, ensuring optimal protein extraction [7]. In this regard, optimal solubilization of membrane proteins has always been a major concern, spurring development of multiple different detergents to supplement/supplant the most widely used, CHAPS (3 [(3-cholamidopropyl) dimethylammonio]-1-propanesulfonate); we have found that simply supplementing the CHAPS-based buffer with lysophosphatidylcholine substantially enhances the extraction and subsequent analysis of membrane proteins, particularly from neural tissue [9].

With an acceptable isolate in hand, the proteome can, as discussed above, be resolved by different techniques. In the case of 2DE, after the proteins are resolved on the second dimension gel, they must be detected. Currently, the favored total protein stain is Sypro Ruby due to its sensitivity, low variation in staining across protein species, and compatibility with subsequent mass spectrometric analysis. However, developments in this area are a major focus, and it is likely that another stain with enhanced sensitivity will be identified and widely used. Following staining, the gel is imaged, and it is this image that is then analyzed using specific software packages; these image analysis programs can warp and match images within sets of gels and then essentially overlay these, and carry out subtractive or differential analysis to identify statistically significant alterations in the proteome. In an effort to get as much information as possible from a single gel, “multiplexing” is gaining in popularity; here at least one other stain specific for a class of proteins (e.g., phosphorylated or glycosylated) is first used to identify select changes in the proteome, and then the total protein pattern is analyzed for more global changes. Proteins of interest are then excised, digested, and analyzed by mass spectrometry, as described above.

Applications in Neuroscience

With respect to Basic research, the use of proteomics has focused largely on the analysis of synaptic vesicles and the post-synaptic density. Here the effort has been to define the protein components and, in some cases, more specifically the phosphoprotein sub-proteome due to the importance of this ►post-translational modification in neural function.

To date, the more widespread application of proteomics has been in the area of Neurological and related disorders [10]. This has included studies on

Alzheimer’s disease, spinal cord injury, muscular dystrophy, Parkinson’s disease, and epilepsy, but this is far from an exhaustive list. The focus has largely been on identifying (phospho)protein alterations that may underlie the susceptibility, progression, or fundamental mechanism of a given disorder. Both in Neuroscience and other Clinical disciplines, the initial goal is most often to identify biomarkers of the condition in question so as to ensure more objective and accurate diagnoses and prognoses. The limitation is clearly accessibility, particularly in terms of acquiring samples from age-matched, “normal” controls; simply put, it is all but impossible to obtain samples from unaffected individuals. Thus, researchers must develop experimental designs that take into account the fact that human neural tissue is an unlikely sample source except in some specific instances of surgery. Although often used, post-mortem sampling must be recognized as insufficient in many regards due principally to the fact that tissue resection generally occurs at variable time intervals after death and that the expression levels of different proteins undergo significant alterations (both increasing and decreasing) during the time that precedes tissue sampling. In most cases though, a more serious and often overlooked caveat is that of disease progression; in most cases, sampling is only possible after clinical diagnosis, and thus after the damage has already occurred. What is to be reasonably learned at this stage? It would thus seem that, without appropriate animal models, much of the application of proteomics to questions in Clinical Neuroscience/Neurology will focus on identifying alterations that occur “after the fact.” Although this is important from the standpoint of understanding the molecular mechanisms of disease progression or recovery from injury, it will unlikely be informative with regard to alterations underlying disease susceptibility and inception. Critical study design and focused application of techniques is mandatory to ensure successful experimental outcomes that will include the identification of effective diagnostic/prognostic biomarkers as well as components underlying fundamental disease mechanisms. This will largely hinge on the analysis of accessible diagnostic biofluids (e.g., cerebrospinal fluid, urine, plasma, and saliva). Thus, coupled with transcriptomics, ►metabolomics, and other, developing, molecular analytical tools, proteomics promises to drive substantial advances in Basic, Clinical, and Translational Neuroscience research.

References

1. Carrette O, Burkhard PR, Sanchez JC, Hochstrasser DF (2006) State-of-the-art two-dimensional gel electrophoresis: a key tool of proteomics research. *Nat Protoc* 1:812–823

2. Olson MT, Epstein JA, Yergey AL (2006) De novo peptide sequencing using exhaustive enumeration of peptide composition. *J Am Soc Mass Spectrom* 17:1041–1049
3. Lohaus C, Nolte A, Blüggel M, Scheer C, Klose J, Gobom J, Schüler A, Wiebringhaus T, Meyer HE, Marcus K (2007) Multidimensional chromatography: a powerful tool for the analysis of membrane proteins in mouse brain. *J Proteome Res* 6:105–113
4. Altelaar AF, Luxembourg SL, McDonnell LA, Liersma SR, Heeren RM (2007) Imaging mass spectrometry at cellular length scales. *Nat Protoc* 2:1185–1196
5. Harris LR, Churchward MA, Butt RH, Coorssen JR (2007) Assessing detection methods for gel-based proteomic analyses. *J Proteome Res* 6:1418–1425
6. Coorssen JR, Blank PS, Albertorio F, Bezrukov L, Kolosova I, Backlund PS Jr., Zimmerberg J (2002) Quantitative femto- to attomole immunodetection of regulated secretory vesicle proteins critical to exocytosis. *Anal Biochem* 307:54–62
7. Butt RH, Coorssen JR (2006) Pre-extraction sample handling by automated frozen disruption significantly improves subsequent proteomic analyses. *J Proteome Res* 5:437–448
8. Butt RH, Coorssen JR (2005) Postfractionation for enhanced proteomic analyses: routine electrophoretic methods increase the resolution of standard 2D-PAGE. *J Proteome Res* 4:982–991
9. Churchward MA, Butt RH, Lang JC, Hsu KK, Coorssen JR (2005) Enhanced detergent extraction for analysis of membrane proteomes by two-dimensional gel electrophoresis. *Proteome Sci* 3:5
10. Drabik A, Bierzynska-Krzysik A, Bodzon-Kulakowska A, Suder P, Kotlinska J, Silberring J (2007) Proteomics in neurosciences. *Mass Spectrom Rev* 26:432–450

Protostome/Deuterostome

Definition

The Deuterostome clade in the animal kingdom including chordates, Hemichordates and Echinoderms.

In Deuterostome animals the Blastopore develops into the anus of the animal. The protostome clade contains most invertebrate phyla. In Protostome animals the Blastopore develops into the mouth of the animal. The Protostome clade is further subdivided into Lophotrochozoans and Ecdysozoans. The Lophotrochozoan clade most animals pass a trochophora-larva stage or use a Lophophor (tentacle like structure). In the Ecdysozoan clade most animals go through a molting process by Ecdysis.

► Evolution of the Brain: Urbilateria

Proust Effect

GORDON M. SHEPHERD¹,
KIRSTEN SHEPHERD-BARR²

¹Department of Neurobiology, Yale University School of Medicine, New Haven, CT, USA

²Faculty of English, Oxford University, Oxford, UK

Definition

“But when from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, taste and smell alone, more fragile but more enduring, more unsubstantial, more persistent, more faithful, remain poised a long time, like souls, remembering, waiting, hoping, amid the ruins of all the rest; and bear unflinchingly, in the tiny and almost impalpable drop of their essence, the vast structure of recollection.” (*Swann's Way*, trans. Moncrieff, 50–51).

The best known example of the power of smell to evoke memories and emotions is the “Proust effect,” as described in the quotation above. This is based on a sensory experience described by Marcel Proust in *Remembrance of Time Past* [1]. The episode involves tasting a small cake dipped in tea, and being suddenly flooded with a childhood memory. The suddenness of the memory, and the strong emotions attached to it, have become symbolic, in both the realm of literary criticism and in sensory physiology, for the power of human taste and smell. Here we review the episode, and show that there is more than meets the eye (and nose).

Characteristics

The Madeleine Incident

Proust's character Marcel is in a depressed mood when he visits his mother. To soothe him she serves him a cup of tea and a madeleine cake. He dips the cake in the tea, tastes it, and is immediately seized by an overwhelming emotion: “an exquisite pleasure had invaded my senses, something isolated, detached, with no suggestion of its origin.” He is aware that behind this is an as yet unidentified memory. After several more tastes and an intense period of searching his memory, he is suddenly transported back to his childhood summers in a seaside resort, Combray, which are associated with happy times. With repeated tasting the power of the memory fades.

The Theory of Pure Memory

In Proust's view, he had uncovered an essential truth about himself, elicited by taste and smell from a “pure memory” unadulterated by being remembered during the intervening years. From this he erected a theory of involuntary (unconscious) versus voluntary

(conscious) memory. Samuel Beckett [2] followed with the view that voluntary (i.e., adulterated) memory cannot recall the exact (i.e., pure) sensation as it was originally experienced. Many literary critics have taken up this view and built on it, regarding it as showing how memory can spring suddenly and purely into mind, triggered after a long period of being forgotten. As a byproduct, they have maintained that conscious autobiographical memory is therefore artificial, a created fiction, compared with true, involuntary memory of the type evoked from the unconscious by the tea-soaked madeleine.

Re-Examining the Theory

We have re-examined Proust's account to test this view [3]. A close textual analysis has revealed that the memory was not sudden, but was the result of considerable effort, as described by the author. Indeed, a page and a half of text is required to describe the repeated efforts of the author to recall the memory. Thus, it appears that as soon as involuntary memory is brought into the arena of consciousness, it too, like voluntary recall, is subjected to similar processes of selection, editing and revision. We have further argued that an understanding of those processes requires knowledge of the neural pathways involved.

What does Neuroscience Tell Us?

Given its iconic status, the madeleine incident thus serves as a useful model for asking: What was happening in Marcel's brain, from the initial sensing of the taste of the tea-soaked madeleine cake to the emotions it called forth, and the memory that finally appeared? Recent research on the sensory mechanisms involved provides several insights that are generally unappreciated even among most neuroscientists.

First, we realize that the smell of an ingested item, cake or otherwise, is due to stimulation of the smell receptors in the nose not by sniffing in, but by breathing out. The volatiles released from the ingested food and liquid at the back of the mouth are carried by exhaled air by the retronasal route through the nasopharynx to reach the receptors (Sun and Halpern, 2005). This olfactory stimulation carries the major part of what appears to be the "taste," but it goes largely unrecognized as smell because it is referred to the mouth where the food and liquid are located. To avoid the confusion, the term "flavor" can be used to refer to the combined sense of taste and smell, as mentioned in the initial quotation from Proust. In fact, flavor also includes all the other senses associated with food intake: touch, pressure, pain, temperature, sound, and even the sight of the food before ingestion.

Second, the olfactory receptor cells connect to the olfactory bulb, where their responses are converted

into spatial activity patterns, called variously odor images or odor maps [4]. Smell perception, by itself or as part of flavor, thus involves discrimination of different spatial images, which also vary with time. We can therefore hypothesize that Proust's effort to identify the memory of the smell of the madeleine involved matching the spatial pattern aroused by that smell with the similar spatial pattern contained in his memory. It may be similar to recognizing complex visual patterns such as faces.

Third, after processing by microcircuits in the olfactory bulb, the odor image is sent to the olfactory cortex, where it is converted by microcircuits into a distributed form called a content-addressable memory [5]. The output of this memory representation has two main destinations. One is to the prefrontal cortex, where it is processed by the highest cognitive centers of the brain [6]. The other is to centers in the limbic system, where emotions are generated. The olfactory pathway has privileged direct access to both these sites; hence the combination of intense emotion and intense cognitive effort experienced by Proust in recollecting the memory of Combray.

Finally, the olfactory pathway contains a series of mechanisms to reduce the stimulation with repeated odor exposure, called adaptation or desensitization, which appear to be reflected in Proust's account of the fading of the sensations with repeated tasting of his madeleine. Rather than intensifying over time, the memory/emotion diminishes with repeated tasting of the triggering stimulus.

The Neural Basis of the Proust Effect

How is the entire memory of Combray recalled from a single sip of tea? This should not be surprising; our cognitive mechanisms have a gestalt quality, in which we perceive and recall things as integrated wholes. According to Nadel and Moscovitch [7], "recovery of remote memories always depends on re-activation of the hippocampal-neocortical complex that constitutes the memory trace." One may hypothesize that this trace, representing the memory of Combray, is distributed in the olfactory cortex and the hippocampal-neocortical complex in a content-addressable form so that a small part of it – the flavor of the madeleine – activates it in its entirety. The brain's ability to fill in the rest of the memory image is turned by Proust into metonym.

Conclusion

We have here summarized only briefly the Proust effect, the literary superstructures built on it, and the recent neuroscience research that gives insight into the relevant brain mechanisms. Further information may be gained from the cited references. The present account may indicate the increasing attraction of this experience as a

model for the brain circuits underlying the power of human senses in general, and the chemical senses in particular. Indeed, the Proust effect may be one of the best instances in which literary criticism can benefit from brain research, and neuroscientists can benefit from literary studies that extend the significance of their experiments into the domain of public discourse.

References

1. Proust M (1987) *A la Recherche du Temps Perdu*. Du Cote de Chez Swann. Flammarion, Paris
2. Beckett S (1931) *Proust*. Grove, New York
3. Shepherd-Barr K, Shepherd GM (1999) Madeleines and neuromodernism: reassessing mechanisms of autobiographical memory in Proust. *Autobiography Stud* 13:40–59
4. Xu FQ, Greer CA, Shepherd GM (2000) Odor maps in the olfactory bulb. *J Comp Neurol* 422:489–495
5. Neville KR, Haberly LB (2004) Olfactory cortex. In: Shepherd GM (ed) *The synaptic organization of the brain*. Oxford University Press, New York, 415–454
6. Rolls ET (2006) Brain mechanisms underlying flavour and appetite. *Philos Trans R Soc Lond B Biol Sci* 361:1123–1136
7. Nadel L, Moscovitch M (1997) Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol* 7:217–227
8. Sun BC, Halpern BP (2005) Identification of air phase retronasal and orthonasal odorant pairs. *Chem Senses* 30:693–706

Pseudo-bulbar Paralysis

Definition

Disease characterized by ►[dysarthria](#), ►[dysphonia](#), ►[dysphagia](#), bifacial ►[paralysis](#), forced crying and laughing, resulting from bilateral lesions of the ►[corticospinal tract](#).

►[Corticospinal Tract](#)

Pseudogene

Definition

Pseudogene is a defunct version of a known gene that has lost its ability to be transcribed.

Pseudohypertrophy

Definition

Increase in limb size not attributed to hypertrophy (increased size) of muscle fibers but due to adipose and connective tissue deposition; occurs in Duchenne Muscular Dystrophy.

►[Duchenne Muscular Dystrophy](#)

Pseudorandom

Definition

A process that appears random but is not. Pseudorandom sequences typically exhibit statistical randomness while being generated by an entirely deterministic computational process.

Pseudotumor Cerebri

Definition

Idiopathic intracranial hypertension (opening pressure >200–250 mmH₂O on CSF examination), with or without papilledema, and/or transient visual obscurations.

Headaches may have a mild to moderate intensity occurring on any part of the head or globally.

►[Headache](#)

Psychedelics

►[Hallucinogens](#)

Psychic Gaze Paresis

Definition

Staring gaze for minutes or sometimes hours, mostly upwards. It cannot be suppressed arbitrarily and is due to unconscious intrapsychical processes.

- ▶ **Psychic Gaze Spasm**
- ▶ **Personality Disorder**

Psychoacoustics

THOMAS N. BUELL¹, CONSTANTINE TRAHOTIS^{1,2},
LESLIE R. BERNSTEIN^{1,2}

¹Department of Neuroscience, University of Connecticut Health Center, Farmington, CT, USA

²Department of Surgery (Otolaryngology), University of Connecticut Health Center, Farmington, CT, USA

Synonyms

Auditory psychophysics; Psychological acoustics

Definition

Psychoacoustics is the area of auditory research in which behavioral methods are used to discern and describe how, and how well, listeners perceive sounds. Combining information obtained from such experiments with corresponding information obtained from physiological and anatomical experiments has resulted in several important descriptions, explanations, and quantitative models of auditory function. Many of the relevant data and phenomena are discussed elsewhere in this volume. Therefore, this discussion is limited to two examples chosen to help the reader understand the kinds of questions addressed by psychoacousticians. In order to provide an intuitive understanding of the field, several practical applications that incorporate knowledge derived from psychophysical experiments will also be highlighted. For further information, the reader is referred to reviews of many pertinent topic areas [1] and two excellent introductory textbooks, one at a more advanced level [2] than the other [3].

Characteristics

Types of Measures

Some experiments in psychoacoustics concern thresholds of detection. They measure the smallest *amounts* of physical stimulation required to produce a reliable

behavioral response indicating that the signal is present. Other experiments concern thresholds of discrimination. Their goal is to measure the smallest *changes* in physical stimulation required for listeners to indicate reliably that two signals are different. Still other, “scaling”, methods use listeners as meters and measure one of a number of perceptual attributes of sound, such as ▶ **loudness** and pitch.

Ties to Physiology

It should be stressed that a comprehensive understanding of hearing also necessarily requires an appreciation of the whole auditory system. Consequently, psychoacousticians have traditionally attempted to understand behavioral data in light of knowledge concerning the anatomy and physiology of the auditory system. We will illustrate such attempts in the context of two important areas of auditory processing; intensity perception and frequency discrimination/▶ **masking**.

Stimulus Intensity

In terms of sensitivity to small changes in intensity, there are two general outcomes to be stated and understood. First, people are quite sensitive to changes in intensity, and can typically discriminate between stimuli differing by about one dB or so. This “just noticeable difference” of 1 dB corresponds to a difference of 25% in acoustic power. In turn, this degree of sensitivity is maintained over about 10–12 orders of magnitude of intensity (i.e. over a range of about 100–120 dB). One goal of psychoacousticians has been to explain this pair of findings in physiological terms. This has proved challenging, because individual neural elements that compose the peripheral auditory nerve have been shown to respond differentially only over the limited and small “dynamic range” of 20–25 dB. To overcome this difficulty, models of intensity perception have focused on ways in which information from a number of individual nerve fibers might be “pooled”. The psychoacoustic and physiological findings are fairly well reconciled, using mathematical models that combine neural responses across small sets of neural elements. Portions of the set of neural elements are characterized as operating over different, albeit limited, ranges of intensity.

In order to understand changes in the perception of loudness, much larger changes of intensity must be considered. For example, it is universally found that one must increase the intensity of a signal by a factor of ten (or 10 dB) in order for it to be judged as “twice as loud”. That is, perceptual increases along a loudness dimension are not “one-to-one” with increases in the physical stimulus, but rather increase at a much slower rate. This empirical outcome, which indicates a high degree of “compression” of the stimulus, has recently

become to be understood at a physiological level. Compression, much like that suggested by the psychoacoustic data has been found in the mechanical-to-neural transduction that occurs in the cochlea. It is of further interest that such peripherally-based effects of compression must also be considered in order to account for a variety of auditory phenomena (see the recent reviews in 4).

Frequency Discrimination and Masking

In a sense, listeners are even more sensitive to changes in frequency than they are to changes in intensity. While the just noticeable increase of 1 dB discussed above corresponds to an increment of 25% in acoustic power, the just noticeable difference for listeners to discriminate between two different frequencies is typically much less. Over the range of frequency extending from about 200 to 8,000 Hz, the just noticeable differences in frequency are found to be less than 0.5%. That is, normal listeners can discriminate between tones of 1,000 and 1,005 Hz, 2,000 and 2,010 Hz, and so on.

A complementary question is how well a listener can analyze or resolve among the set of frequencies composing complex sounds (including noise, speech, music, etc). In effect, psychoacousticians determine how well a listener can “pick out” the presence of the particular frequency or set of frequencies that define the “signal”. A classic type of experiment asks how intense a signal must be in order to be detected when it is presented along with a potentially obscuring background sound, the “masker”. The number and variety of psychoacoustic experiments investigating such questions is remarkably large and constitutes the bulk of the published work in the field. One time-honored finding is that only a small fraction of frequency components composing the background masker actually affects detection of a tonal signal. For example, the detectability of a 1,000-Hz tone is determined by only the 160 Hz-wide portions of the masker that immediately surround the signal. That is, one can add or subtract large amounts of acoustic energy outside that region and not affect the signal’s detectability. This means that other attributes of the masker, including its loudness and pitch, do not, by themselves, determine the degree of masking. It is handy to know that the bandwidth of the frequencies that are “critical” for masking tonal signals (nowadays termed the auditory filter) is approximately 16% of the frequency of the signal to be detected.

The links to physiology in these realms are both strong and pervasive. First and foremost, a “place” mapping of frequency exists within the cochlea, in that it is most sensitive to higher frequencies in its more basal portions, and most sensitive to lower frequencies in its more apical portions. This place mapping is preserved and reiterated throughout the auditory nervous

system, including the auditory cortex. In addition, the frequency-tuning characteristics, or bandwidths, of individual nerve fibers are commensurate with the widths of psychoacoustically-determined auditory filters as a function of frequency. A second encoding of frequency is provided in the timing of neural discharges. That is, the time between neural discharges becomes smaller and smaller as the frequency of the signal is increased.

Many auditory scientists have debated the relative salience of place vs. time codes, while modeling a number of important auditory phenomena including frequency discrimination, masking, and the perception of pitch. Over time, one or the other view has been found to prevail. In our judgment, neither the acceptance nor the rejection of one of the two candidate codes may be logically possible, because changes in “place” and changes in “neural timing” both occur concomitantly as frequency is changed.

Applications

Knowledge and techniques derived from psychoacoustic research are relevant and useful in a variety of practical endeavors. While many applications may be familiar to us all (e.g., the design of telephones for the efficient transmission and understanding of speech), others are much less apparent. Beginning with the familiar, many of the basic findings from psychoacoustic research have been used to define and depict “normal hearing.” Such findings, in turn, have been used to create and refine tests of hearing that are used in many ways to aid in the diagnosis and treatment of various kinds of hearing impairment. Otolaryngologists and audiologists use such information in order to differentiate among various hearing deficits, and in the selection and fitting of patient-appropriate hearing aids. For more than a decade, psychoacousticians have played an integral part in the development, design, understanding and evaluation of complex issues surrounding the use of cochlear implants. Knowledge from psychoacoustics has also proved beneficial in all phases of the discovery and application of specialized, non-invasive screening tests of infant hearing. Similar types of tests and guidelines have been usefully applied in industrial and governmental settings, both as part of hearing conservation programs and to develop standards concerning acceptable occupational and community noise levels.

Knowledge obtained from psychoacoustics has always been useful in designing and evaluating high-fidelity sound systems. Today, because of advances in computing power and miniaturization, psychoacoustic data have become highly relevant, if not ubiquitous. For example, one can purchase inexpensive devices that digitally store incredibly large amounts of music. This is possible because psychoacousticians and electrical engineers found ways of using knowledge concerning auditory

sensitivity in order to greatly reduce the amounts of information required for satisfying reproduction. Specifically, only the necessary information, on a moment-by-moment basis, is preserved. Success of this technique is evidenced by the fact that listeners are typically unaware that the original sound has been modified. The same types of algorithms have also proved useful in the transmission of music and speech. These include the schemes used to send audio information to cellular telephones, satellite and digital television and radio devices and over the internet.

Another important arena for application of psychoacoustics is the concert hall. Here the thrust has been first to understand what physical variables differentiate successful concert halls from less successful ones. Such knowledge has been used to establish psychoacoustic-related dimensions that guide the design and determine the perceived quality of the halls. Finally, computer-based systems now exist that enable the designer to simulate candidate designs and to “preview” them. Similar schemes and technology are being applied to other aspects of architectural acoustics including improvements in the design of highly reverberant spaces such as churches and classrooms.

References

1. Crocker MJ (1997) Encyclopedia of acoustics, vol 3. Wiley, New York
2. Moore BCJ (2003) An introduction to the psychology of hearing, 5th edn, Academic Press, San Diego, CA
3. Yost WA (2000) Fundamentals of hearing: an introduction, 4th edn. Academic Press, San Diego, CA
4. Bacon SP, Fay RR, Popper AN (eds) (2004) Compression: from cochlea to cochlear implants, Springer handbook of auditory research, vol 17. Springer Verlag, New York

Psychogenic

Definition

Psychogenic refers to phenomena arising from thought processes.

Psychological Acoustics

► Psychoacoustics

Psychometric Curve/Psychometric Function

Definition

Relationship between physical properties of a stimulus and a measured behavior. Typically these take the form of a sigmoid function in which low levels of stimulus produce a small psychophysical result and at some point increases produce a faster rise in response, which saturates at high stimulus levels.

Psychomotor Seizures (Temporal-lobe Seizures)

Definition

► Complex Partial Seizures (Temporal-lobe or Psychomotor Seizures)

Psychopathic Personality

► Personality Disorder

Psychopathy

Persons who often exhibit aggressive behavior and try to achieve their personal aims by illegal actions and criminal lifestyle.

► Forensic Neuropsychiatry

Psychopharmacology

► Behavioral Neuropharmacology

Psychophysics

WALTER H. EHRENSTEIN

Leibniz Research Center for Working Environment and Human Factors, University of Dortmund, Dortmund, Germany

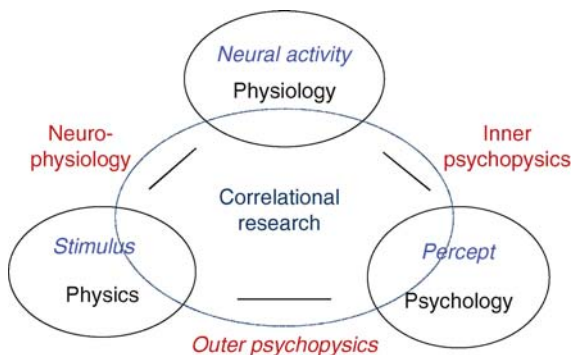
Synonyms

Phenophysics

Definition

Psychophysics, as first established by Gustav Theodor Fechner in 1860, concerns the science of the relations between body and mind, or, to put it more precisely, between *physical* and *phenomenal* worlds [1–6]. Objectively we have physical events as reflected by brain processes, subjectively these processes appear as processes of our mind. Fechner already distinguished between *inner psychophysics* or the relation of sensory experience to its corresponding neural activity, and *outer psychophysics*, which deals with the relation between percepts and variations of the ►stimulus itself (see Fig. 1).

For much of the century following Fechner's publication of *Psychophysik* in 1860, inner psychophysics remained just a theoretical option until objective methods for the study of brain functions became available. Thus, outer psychophysics has shaped not only the development of experimental psychology and phenomenology



Psychophysics. Figure 1 *Interdisciplinary setting of psychophysics:* Percepts are related to corresponding physical stimulus properties (*outer psychophysics*) or to corresponding neural activity (*inner psychophysics*). For a long time inner psychophysics remained a merely theoretical concept, whereas outer psychophysics provided the basis for methods to study sensory and brain processes. Now various objective methods afford a direct study of sensory and brain processes. This has made possible a new interplay between classic psychophysics and modern neuroscience that has come to be called ►correlational research [2,7].

[1,6], but also of sensory physiology, affording its pioneers (Aubert, Exner, Helmholtz, Hering, von Kries, Mach, Purkinje, Weber) to gain basic insights into sensory mechanisms [2–4]. Today, sensory and brain processes can be investigated by objective methods such as electrophysiology (single-unit recordings, EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and positron emission tomography (PET). The relative ease of use and non-invasiveness of most of these techniques has made a new interplay between classic psychophysics and modern neuroscience possible. The complementary research approach that concerns itself with subjective and objective correlates of sensory and neural processes has come to be called ►correlational research [2,7], see Fig. 1.

Description of the Theory

Psychophysics accounts for the problem of measuring sensory experience by closely linking percepts to physical stimuli. No apparatus is necessary to obtain percepts; they are immediately present and available to each of us. The problem is thus not how to obtain sensory experience, but how to describe and investigate individual percepts so that they can be reliably communicated. An investigation might begin with a simple question such as “can you hear the tone?”. This task requires *detection*. If we want to further determine which stimulus characteristics an observer can sense (e.g., the quality or spatial location of a sound), we arrive at the problem of *identification*. Detection and identification are solved quickly and almost simultaneously when the stimuli are strong and clear. However, under conditions of weak and noisy signals we often experience a stage at which we first detect only that something is there, but fail to identify what or where it is, exactly. In such a situation we try to filter out the consistent signal attributes, for instance, the sound of an approaching car, from inconsistent background noise. This task requires *discrimination* of the stimulus, or signal, from a noisy background, and the task is performed under uncertainty. As the car approaches and its sound becomes stronger, the probability of correct discrimination between signal and noise is enhanced. Even if we clearly detect and identify an object, we may still be faced with a further problem of ►perception, such as: “Is this car dangerously close?” or “Is the rattle under the hood louder than normal?” Questions such as these, concerning “How much x is there?”, are part of another fundamental perceptual issue, that of *scaling*, i.e. to locate the magnitude of the stimulus on a psychophysical scale.

►Characteristics

Quantitative Laws of Psychophysics

Psychophysics emerged out of the contributions of the sensory physiologist E. H. Weber (1795–1878) who

established perception as an experimental rather than observational discipline. Working with the discrimination of lifted weights, he demonstrated that the smallest difference between two weights (ΔI) which we can distinguish by way of feeling changes in muscle tension was a constant fraction (k) of the reference weight (I):

$$\Delta I/I = k \text{ (Weber's law)}$$

For example, if an increase of 1 g is needed in order to just experience that a weight is heavier than its reference of 40 g, an increase of 10 g would already be required for a weight to just appear heavier if its reference is 400 g. Accepting the validity of Weber's law, Fechner assumed that equal stimulus differences corresponded to equal perceptual differences or units. Sensory magnitudes could be assigned values according to the number of just noticeable differences. Inspired by Leibniz's concept of subliminal units of experience (*petites perceptions* or minute percepts as differential units of experience), Fechner postulated a relation between infinitesimal increase of stimulus intensity (dI) and corresponding subliminal increase in perceptual intensity (dS), by deriving his fundamental formula: $dS = dI/I$. By integration we obtain a logarithmic relation between stimulus and sensation:

$$S = c \log I \text{ (Fechner's law)}$$

where S is the subjective and I the objective intensity and c refers to a constant depending on the respective sensory modality.

Fechner's law roughly predicts that a doubling of perceived intensity requires a 10 times increase of physical intensity. It holds pretty well for stimulus intensities in a middle range of the stimulus dimension. With very low or very high stimulus intensities, however, observed and predicted values deviate markedly. As an alternative to threshold measurements supra-threshold psychophysical scaling procedures were already developed by Tobias Mayer in 1754 [4] and more systematically later by J. A. F. Plateau (1872) and Delboeuf (1873, 1875) who studied the lightness of different gray levels. S. S. Stevens [10] popularized scaling procedures, especially the procedure of magnitude estimation, in which the experimenter assigns a value to a standard stimulus, e.g., the number 100, and the observers then rate the magnitude of other stimuli in proportion to the standard. So, if a stimulus appears half or twice as intense as the standard, it would be given the numbers 50 or 200, respectively. The results obtained with these and other direct scaling methods, such as ►cross-modality matching, are best described by a power function:

$$S = c I^n \text{ (Stevens's law)}$$

where S is scaled sensory intensity, c is a constant, I is physical intensity, and n is an exponent that varies for different sensory continua.

Psychophysical Methods

The most basic function of any sensory system is to detect changes of energy which can consist of chemical (taste, smell), *electromagnetic* (vision), *mechanical* (audition, proprioception, touch) or *thermal* events. In order to be noticed, the stimulus has to reach a minimal amount of stimulus intensity that, according to Fechner [3], "lifts its sensation over the threshold of consciousness." This is the *absolute threshold*, which is the intensity an observer can just barely detect, whereas the *difference threshold* is based on stimulus intensities above the absolute threshold and refers to the minimum intensity by which a variable or *comparison* stimulus must deviate from a constant or *standard* stimulus to produce a just noticeable difference in perception.

Method of Adjustment

The easiest way to determine thresholds is to let a subject adjust the stimulus intensity until it is just noticed or until it just becomes unnoticeable (absolute threshold); or until it appears to be just noticeably different from, or to just match some other standard stimulus (difference threshold). The observer is typically provided with a control of some sort that can be used to adjust the intensity, say of a sound, until it just becomes audible (or louder than a standard sound), and then the stimulus intensity is recorded to provide one estimate of the observer's threshold. Alternatively, the observer can adjust the sound from clearly audible to just barely inaudible (or to match the standard sound), providing another estimate of the threshold. Typically, the two series of measurement, one in which the signal strength is increased (ascending series) and one of decreasing signal strengths (descending series) are alternated several times and the results are averaged to obtain the threshold estimate. For example, if a tone is first heard at 5.0 or 5.5 dB on two ascending trials and first not heard at 4 or 4.5 dB on two descending trials, the resulting threshold estimate is 4.75 dB.

Method of Limits

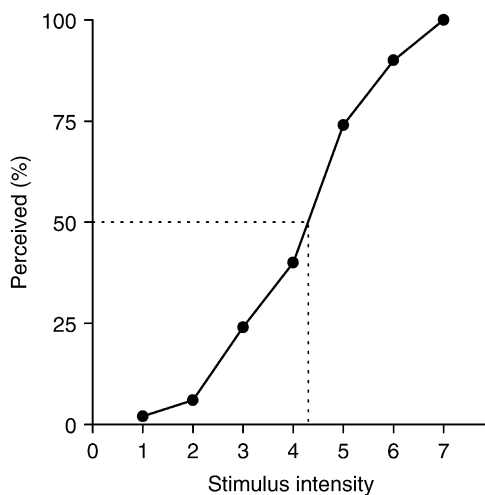
In the ►method of limits the stimulus is varied by the experimenter (or a computer program) and the observer's response is recorded to each stimulus presentation. As in the previous method, the stimulus should initially be too weak to be detected and increased until it is perceived (ascending trials). Conversely in a descending trial, stimulus intensity, say a light, is reduced from clearly seen until it becomes invisible.

Method of Constant Stimuli

In the ►method of constant stimuli the experimenter selects a number of stimulus values (usually from five to nine) which, on the basis of previous exploration (e.g., using the ►Method of Adjustment), are likely to encompass the threshold value. This fixed set of stimuli

is presented multiple times in a quasi-random order that ensures each will occur equally often. After each stimulus presentation, the observer reports whether or not the stimulus was detected (for the absolute threshold) or whether its intensity was stronger or weaker than that of a standard (for computing a difference threshold). Once each stimulus intensity has been presented multiple times (usually not less than 20), the proportion of “detected” and “not detected” (or, “stronger” and “weaker”) responses is calculated for each stimulus level. The data are then plotted with stimulus intensity along the abscissa and percentage of perceived stimuli along the ordinate (see Fig. 2).

If there was a fixed threshold for detection, the psychophysical function should show an abrupt transition from “not perceived” (0%) to “perceived” (100%). Psychometric functions, however, seldom conform to this all-or-none rule. We usually obtain a sigmoid (S-shaped) curve that reflects that lower stimulus intensities are detected occasionally and higher values more often, with intensities in the intermediate region being detected on some trials but not on others. There are various reasons for obtaining an S-shaped rather than a sharp step function. A major source of variability is the continual fluctuations in sensitivity that occur in any biological sensory system (due to spontaneous activity or internal noise). Those inherent fluctuations mean that activity elicited by external stimulation is to be detected against a background level of activity. The threshold sensation that occurs with a certain *probability* can be defined statistically. By convention, the absolute threshold measured with the



Psychophysics. Figure 2 Psychophysical function which shows the relationship between the percentage of times that a stimulus is perceived and the corresponding stimulus intensity. The threshold is defined as the intensity at which the stimulus is detected 50% of the time [2].

method of constant stimuli is defined as the intensity value that elicits “perceived” responses on 50% of the trials. Notice that in the example shown in Fig. 2, no stimulus level was detected on exactly 50% of the trials. However, level 4 was detected in 40% and level 5 in 74% of the trials. Consequently, the threshold value of 50% lies between these two points. If we assume that the percentage of trials in which the stimulus is detected increases linearly between these intensities (which is not unreasonable given that sigmoid functions are approximately linear in the middle range), we can determine the threshold intensity by linear interpolation as follows:

$$T = a + (b - a) \cdot \frac{50 - p_a}{p_b - p_a},$$

where T is the threshold, a and b are the intensity levels of the stimuli that bracket 50% detection (with a being the lower intensity stimulus), and p_a and p_b the respective percentages of detection. For the present case we obtain the following result:

$$T = 4 + (5 - 4) \cdot \frac{50 - 40}{74 - 40} = 4 + \frac{10}{34} = 4.29.$$

Although the method of constant stimuli is assumed to provide the most reliable threshold estimates, its major drawback is that it is rather time consuming and requires a patient, attentive observer because of the many trials required.

Adaptive Testing

Adaptive testing procedures are used to keep the test stimuli close to the threshold by adapting the sequence of stimulus presentations according to the observer’s response. Since a smaller range of stimuli needs to be presented, adaptive methods are relatively efficient. Adaptive procedures were first introduced by Georg von Békésy in 1947, who applied his [staircase method](#) to audiometry [2]. The staircase method is a modification of the Method of Limits. As long as the observer says “yes” (I perceive) stimulus intensity is decreased by one step, until the stimulus becomes too weak to be detected. At this point we do not, as in the method of limits, end the series, but rather reverse its direction by increasing the stimulus intensity by one step. This continues with increasing the intensity if the observer’s response is “no” and decreasing the intensity if it is “yes.” In this way, the stimulus intensity flips back and forth around the threshold value. Usually six to nine such reversals in intensity are taken to estimate the threshold, which is defined as the average of all the stimulus intensities at which the observer’s responses changed.

Research Fields and Applications

Psychophysics allows investigation of how living creatures perceive sensory stimuli in relation to their environmental setting as well as to compare the

phenomenal worlds of humans with closely related species (monkey, cat) or even fairly distant species (birds, insects). Comparative relational psychophysical research across different species and across different stages of development provides the intriguing option of an integrated framework of behavioral and brain research [9]. For instance, the combined psychophysical and electrophysiological study of sensory performance has established the concept of the **perceptive field** as psychophysical counterpart of receptive field organization with the conjecture that perceptual organization is largely determined by single-cell activity. Meanwhile, various perceptual properties, including contrast of brightness, color, orientation, and motion as well as Gestalt phenomena, such as illusory contours or border-ownership, have been shown to be linked to the highly specialized functions of receptive fields at various levels of the visual system [7]. Furthermore, computer-assisted adaptive psychophysical methods are increasingly used in clinical routine diagnostics to assess impairment of sensory and neuropsychological function [1,2]. Psychophysics can also assist in elementary decisions of daily life. For example, scaling of auditory intensity can provide firm evidence for the effectiveness of noise protection measures. Industrial and ergonomic norms, such as of lighting on streets or at workplaces, or individual norms, e.g., accounting for age-dependent changes of sensory performance, are or are to be based on psychophysical evaluation. Consequently, psychophysics is of utmost importance for the approach of Human Factors [10], a joint profession of engineers and psychologists to design and evaluate simple and complex systems in order to optimize working and life conditions.

References

- Ehrenstein WH (2003) Psychophysik. In: Neuser-von Oettingen K (ed) *Psychologie von A–Z: Die wichtigsten 60 Disziplinen*, Spektrum, Heidelberg, pp 156–159
- Ehrenstein WH, Ehrenstein A (1999) Psychophysical methods. In: Windhorst U, Johansson H (eds) *Modern techniques in neuroscience research*. Springer, Berlin Heidelberg New York, pp 1211–1241
- Fechner GT (1860/1966) *Elemente der Psychophysik*. Leipzig: Breitkopf & Härtel (reprinted in 1964 by Bonset, Amsterdam); English translation by HE Adler (1966): *Elements of psychophysics*. Holt, Rinehart & Winston, New York
- Grüsser OJ (1993) The discovery of the psychophysical power law by Tobias Mayer in 1754 and the psychophysical hyperbolic law by Ewald Hering in 1874. *Behav Brain Sci* 16:142–144
- Hensel H (1974) Thermoreceptors. *Ann Rev Physiol* 36:234–249
- Horst S (2005) Phenomenology and psychophysics. *Phenomenol Cogn Sci* 4:1–21
- Spillmann L (2006) From perceptive fields to Gestalt. *Prog Brain Res* 155:67–92
- Stevens SS (1975) *Psychophysics: introduction to its perceptual, neural, and social prospects*. Wiley, New York
- Sarris V (2006) *Relational psychophysics in humans and animals. A comparative-developmental approach*. Psychology Press, Hove & New York
- Proctor RW, Van Zandt T (2008) *Human factors in simple and complex systems*, 2nd edn, CRC Press, Boca Raton, FL

Psychostimulants

► Stimulants

Psychotic Features

Definition

These include delusions (irrational thoughts and fears) and hallucinations (seeing or hearing things that are not really there). Often psychotically depressed people become paranoid or come to believe that their thoughts are not their own (thought insertion) or that others can “hear” their thoughts (thought broadcasting). People with psychotic depression are usually aware that these thoughts are not true.

► Major Depressive Disorder

Psychotomimetics

► Hallucinogens

Pterosaurs

Definition

Extinct flying reptiles (e.g. Pterodactylus, Pteranodon, Quetzalcoatlus, etc.), not ancestors of birds.

► Evolution, of the Brain: At the Reptile-Bird Transition

Ptosis

Definition

Drooping of the upper eyelid from paralysis of the third nerve.

► Endocrine Disorders of Development and Growth

Pudendal Nerve

Definition

A somatic nerve with cell bodies of the motoneurons located in Onuf's nucleus in the S2-S4 spinal segments; contains afferent and efferent pathways to the urethral and anal sphincters and afferent innervation to the perineum, urethra and the sex organs (penis and clitoris).

► Micturition
► Neurophysiology of Sexual Spinal Reflexes

Pulleys

Definition

When the eyes move from the primary position, the eye muscles do not slide freely within the orbital tissue.

Instead their paths are restricted, possibly by rings of connective tissue and smooth muscle that have been termed orbital pulleys.

► Eye Orbital Mechanics

Pulmonary Reflexes

► Respiratory Reflexes

Pulvinar

Definition

A component of the thalamus, relatively enlarged in carnivores and primates. It deals with salience (visual

salience) and is involved in selective attention. It is reciprocally connected with much of the cerebral cortex. Its inferior and lateral parts also receive input from the superior colliculus. The homologous structure in lower animals is the Lateral Posterior thalamic group (LP-Pulvinar).

► Visual Attention
► Visual Role of the Pulvinar

Punisher

Definition

A punisher is any stimulus an animal will work to avoid, such as somatosensory pain, foot shock, timeout, or an unpleasant taste. In humans, monetary loss may also act as a punisher.

► Value-based Learning

Punishment

Definition

Punishment is a procedure whereby an aversive event (usually pain) following a response causes the reduction of that response. Punishment is considered by some behavioral psychologists to be a “primary process” – a completely independent phenomenon of learning, distinct from reinforcement.

► Aversive Learning

Pupillary Light Reflexes

Definition

Constriction of the pupils in response to increased light falling onto the retina. When light is shone on one retina, the pupil of the same eye constricts (direct response) as well as the pupil of the other eye (consensual response).

► Consensual Light Reflex
► Pretectal Nuclei
► Neural Regulation of the Pupil

Purinergic Receptors

Definition

Purinergic receptors are receptors that respond to adenosine triphosphate (ATP) and related agents.

Metabotropic (G-protein coupled receptors, P2Y) and ionotropic receptors (ion channels, P2X) have been identified. Excitatory P2X receptors are present in urinary bladder smooth muscle (P2X1) and in bladder afferent nerves (P2X2/3).

► **G-protein Coupled Receptors (GPCRs): Key Players in the Detection of Sensory and Cell-Cell Communication Messages**

Purinergic Receptors in Urinary Bladder

Definition

Excitatory P2X receptors are present in urinary bladder smooth muscle (P2X1) and in bladder afferent nerves (P2X2/3).

► **Micturition**
► **Purinergic Receptors**

Purkinje Cell, Neuron

Definition

Large, pear-shaped, GABAergic neuron located in the cerebellar cortex characterized by an intricate dendritic arbour and many dendritic spines.

The Purkinje cell sends the sole output from the cerebellar cortex. It receives excitatory synaptic inputs from parallel and climbing fibers and inhibitory synaptic inputs from basket, stellate, and other Purkinje neurons, and sends inhibitory outputs to the cerebellar or vestibular nucleus.

► **Cerebellum**
► **Cerebellar Functions**

Pursuit Eye Movement

Definition

An eye movement that matches the speed and direction of the eye to that of a moving target.

► **Pursuit-Saccade Coordination**

Pursuit-Saccade Coordination

ROBERT H. WURTZ

Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Definition

Rapid or saccadic eye movements (► **saccade**, ► **saccadic eye movement**) allow us to shift our gaze from one part of a visual scene to another. This allows us to position objects in the scene of greatest interest on the region of the retina with the highest resolution, the central or foveal region. For example, we would make these saccadic eye movements several times per second as we looked out of a window onto a busy street scene. Smooth ► **pursuit eye movements** allow us to keep the fovea on objects that are moving so that we can have the sharpest vision of these objects in spite of their motion. As we look out the window, these pursuit eye movements would allow us to keep a person's face centered on the fovea even though they were walking along as we watched them. We can also make a saccade to the walking person and then immediately use the pursuit eye movements to keep that person's image on our fovea. As we continually use both of these eye movements in our everyday vision, these eye movements must be coordinated and the brain mechanisms underlying this coordination are beginning to be understood.

Characteristics

Upstream Event/Conditions

Control of saccadic eye movements depends upon a circuit within the brain that extends from the highest levels of visual processing in the cerebral cortex, to the neurons connecting to the eye muscles that lie in the midbrain and pons in the brainstem [1] The cortical areas devoted to this processing are centered in the lateral intraparietal area of parietal cortex and the frontal eye field area of frontal cortex. Both areas project to the brainstem, particularly to the structure on the roof of

the brainstem, the ►superior colliculus (SC). Another pathway from the cortex passes through the basal ganglia to the superior colliculus. Pursuit eye movements also depend on activity in cerebral cortex for a critical feature of their function: the determination of the speed and direction of the object that is about to be followed by the eye. Areas providing this information are also distributed in cortex, but are concentrated in the visual region of cortex referred to as the middle temporal area and the medial superior temporal area, and in the frontal eye field in a region distinct from that related to saccadic eye movements. The processing related to saccades and to pursuit appears to be kept separate in the cerebral cortex.

Downstream Events/Condition

The generation of saccades requires connections to nuclei in the midbrain and pontine reticular formations, which in turn connect to the motor neurons that innervate the eye muscles [1]. The connections necessary for pursuit eye movements are conveyed to visuomotor nuclei in the pons, primarily the dorsolateral pontine nuclei. The pathway reaches the oculomotor neurons via projections through the cerebellum to the vestibular nucleus.

Involved Structures

The superior colliculus has a representation of the visual field spread out in each of its major layers [2]. In the superficial layers the neurons respond to visual stimulation, and in the intermediate layers the neurons are active before eye movements to that part of the visual field where the visual stimulation is located. The collicular neurons are organized into a map of the contralateral visual field, so that each neuron is active in relation to visual stimulation or eye movement in just one region of the visual field. It is in the intermediate layers that there is evidence for the coordination between saccades and pursuit. The intermediate layer neurons not only increase their discharge just before the saccade (or more generally an eye and head movement), but they show a buildup of activity that precedes that burst [3,4]. This buildup or prelude activity occurs whether or not the saccade related to the target actually occurs. If the saccade does occur, the buildup activity blends into the burst of activity preceding the saccade. If the saccade is not made, the activity decreases. Thus, the buildup activity can be largely independent of the actual generation of the movement, and it seems to be related to what must necessarily precede the movement including target selection.

One possibility is that the buildup activity simply indicates that there is an error between where the eye is looking now and where the target for the next eye movement is located – an error signal, not a saccadic movement signal. That is, each neuron on this map

might indicate the error between where the eye is and where the target is, with large differences in the caudal colliculus and smaller ones in the rostral colliculus [5]. If the difference between where the eye is looking is very small (a fraction of a degree visual angle), the monkey frequently does not make any saccade. This activity has been referred to as fixation activity, but the most parsimonious interpretation of the activity is that it is the same buildup activity seen throughout the colliculus. The difference in eye and target position is just small, the error is small, and no movement need be made. With slightly larger errors, the buildup activity precedes a saccade to the target. If the target is moving, the monkey might make a not a saccade but a pursuit movement to the target, and this pursuit movement is also preceded by the increased buildup neuron activity [6]. Increased activity for both pursuit and saccades occurs only for movements in the visual field contralateral to the colliculus in which the neuron is found. Thus, the buildup neurons can be regarded as a shared error signal available to both the pursuit and the saccadic system, and this type of shared signal has been proposed as part of the mechanisms that coordinate these two movements. Further evidence supporting this view comes from experiments which showed that electrical stimulation or chemical inactivation altered pursuit eye movements [7]. Activity of the neurons can also predict the timing of pursuit as well as saccadic eye movements [8]. Thus, the same neurons that are involved in the preparation to make saccades might also contribute to the preparation to initiate pursuit. The test of this view would be to verify this pursuit – saccade interaction at points in the pathway after the signals for movement leave the superior colliculus, but this remains to be done.

Methods to Measure This Event/Condition

All of the observations described are derived from single neuron recording in awake behaving monkeys who select the targets and move their eyes to them [9]. The monkeys are trained on tasks that allow the comparison of neuronal activity to the same behavior on a series of similar movements, and this reveals the consistency of the relationship of the neuronal activity and the eye movement behavior. The eye movements are recorded using a precise method for recording eye position, velocity and acceleration. The monkey's behavior is controlled by online computer systems that also collect and store all the data from the experiments.

References

1. Krauzlis RJ (2004) Recasting the smooth pursuit eye movement system. *J Neurophysiol* 91:591–603
2. Sparks DL, Hartwich-Young R (1989) The neurobiology of saccadic eye movements. The deep layers of the superior colliculus. *Rev Oculomot Res* 3:213–256

3. Glimcher PW, Sparks DL (1992) Movement selection in advance of action in the superior colliculus. *Nature* 355:542–545
4. Munoz DP, Wurtz RH (1995) Saccade-related activity in monkey superior colliculus. I. Characteristics of burst and buildup cells. *J Neurophysiol* 73:2313–2333
5. Wurtz RH, Basso MA, Paré M, Sommer MA (1998) Contributions of the superior colliculus to the cognitive control of movement. In: Gazzaniga MS (ed) *The cognitive neurosciences*, MIT Press, Cambridge, pp 573–587
6. Krauzlis RJ, Basso MA, Wurtz RH (2000) Discharge properties of neurons in the rostral superior colliculus of the monkey during smooth-pursuit eye movements. *J Neurophysiol* 84:876–891
7. Basso MA, Krauzlis RJ, Wurtz RH (2000) Activation and inactivation of rostral superior colliculus neurons during smooth-pursuit eye movements in monkeys. *J Neurophysiol* 84:892–908
8. Krauzlis R, Dill N (2002) Neural correlates of target choice for pursuit and saccades in the primate superior colliculus. *Neuron* 35:355–363
9. Wurtz RH, Goldberg ME (1972) Activity of superior colliculus in behaving monkey. III. Cells discharging before eye movements *J Neurophysiol* 35:575–586

Putamen

Definition

The caudate nucleus and putamen together form the corpus striatum. Both are derived ontogenetically from the same anlagen, but are separated by incoming fibers from the internal capsule.

The corpus striatum is an important inhibitory component of motor movement programs and has manifold connections with the globus pallidus, substantia nigra and the motor cortex.

- Basal Ganglia
- Striatopallidum
- Telencephalon

Pyramidal

Definition

Refers to the triangular shape of an object; in neuroscience either to the shape of neocortical cell bodies in various laminae, or to the shape of the tract in the medulla oblongata of humans that is made up of

axons derived from cortical upper motor neurons and destined for the spinal cord as the cortico-spinal path.

- Evolution of the Wulst

Pyramidal Decussation

Synonyms

- Decussatio pyramidum; ► Decussation of pyramids

Definition

In the pyramidal decussation, 70–90% of the pyramidal tract decussate to the contralateral side. The decussation lies directly below the pyramid (of the myelencephalon), in the middle of the myelencephalon. The decussation joins the lateral pyramidal tract.

- Myelencephalon

Pyramidal System Organization

- Motor Cortex: Output Properties and Organization

Pyramidal Tract

Synonyms

- Tractus pyramidalis

Definition

The largest descending motor tract is formed by the axons of the pyramidal cells of the motor cortex and is thus called the pyramidal tract. It courses nonstop from the cortex to the corresponding segments in the spinal cord, explaining why it is also called the corticospinal tract. At the upper margin of the myelencephalon, this tract rises to the surface as the pyramid (of myelencephalon).

70–90% of the fibers then cross in the pyramidal decussation to the contralateral side, and continue to run in the spinal cord as the lateral pyramidal tract. The remaining fibers descend in the medial pyramidal tract. The fibers project directly or indirectly to the alpha

motoneurons, especially of the distal extremities (hand/forearm), hence the pyramidal tract plays a vital role in fine motor control.

- ▶Corticospinal Neurons
- ▶Motor Cortex: Output Properties and Organization

Pyramidotomy

Definition

The act of sectioning the pyramidal tract.

- ▶Motor Cortex: Output Properties and Organization
- ▶Pyramidal Tract

Pyrexia, Hyperpyrexia

- ▶Endotoxic Fever

Pyridoxine Intoxication

Definition

Overdose intake of pyridoxine may lead to chronic ▶sensory polyneuropathy, with symptoms of

numbness, tingling and pain in the extremities, and sensory ataxia.

Pyridoxine (Vitamin B6) Deficiency

Definition

Not a common disorder anymore, except in the elderly populations, where it may be associated with impaired cognitive function, ▶Alzheimer's disease, cardiovascular disease, and some types of cancer.

- ▶Alzheimer's Disease

Pyriform Cortex

- ▶Olfactory Cortex

Pythons

Definition

A group of giant snakes (Boidae) in Africa and South-Asia.

- ▶Evolution, of the Brain: At the Reptile-Bird Transition